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Optimization-based approaches to augment the value of integrated decision-making in the chemical-pharmaceutical industry

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"The good life is one inspired by love and guided by knowledge."

Bertrand Russell

in *What I Believe (1925),* Chapter 2: The Good Life

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Finalmente, ao Miguel, à Lara e à Lia, agradeço a inspiração que trago comigo.

Resumo

Nos últimos anos, o contexto de negócios no qual a indústria de processos opera mudou drasticamente, tornando-se mais desafiante e competitivo de um ponto de vista operacional. No caso particular da indústria farmacêutica, a diminuição do tempo de vida efetivo das patentes e o subsequente aumento da concorrência por parte dos medicamentos genéricos impulsionaram, tanto a indústria como a investigação, a perseguir novas estratégias de desenvolvimento e produção. Não só o tempo necessário para colocação de novos produtos no mercado se tornou uma questão central, mas também aspetos de sustentabilidade como a utilização eficiente dos recursos disponíveis e a gestão de resíduos, potenciaram o desenvolvimento de abordagens inovadoras baseadas em otimização para alcançar a excelência operacional.

Novas estratégias para aumentar a capacidade de resposta das empresas e a sua competitividade devem combinar decisões tomadas durante o ciclo de desenvolvimento de novos medicamentos com decisões de produção. Estas abordagens requerem a integração de decisões de longo- e curto-prazo, abrangendo problemas complexos que englobam não só múltiplos níveis hierárquicos, mas também diferentes escalas de tempo e espaço dependentes entre si. Neste contexto, métodos de otimização bem estabelecidos, focados exclusivamente em problemas de planeamento e escalonamento de produção, já não são adequados, pois geralmente negligenciam as incertezas e os riscos associados à interdependência entre decisões e ignoram requisitos de sustentabilidade e flexibilidade do contexto de negócios atual. Apesar de algumas contribuições importantes já terem sido apresentadas abordando a integração de vários níveis de decisões, o desenvolvimento de uma metodologia eficaz permanece ainda como um importante desafio de investigação. Para melhorar significativamente o desempenho geral dos sistemas, devem ser consideradas abordagens holísticas coordenadas e multifuncionais. Dessa forma, soluções globalmente otimizadas que efetivamente apoiarão a estratégia de negócios serão alcançadas.

Este trabalho de investigação pretende, assim, preencher esta lacuna, compreendendo as fragilidades operacionais do setor e explorando o real valor e impacto de uma tomada de decisão integrada, considerando aspetos como a variabilidade da procura e diversidade de produtos, a incerteza associada a cada nível de decisão e questões de sustentabilidade. O principal objetivo desta investigação é desenvolver abordagens baseadas em otimização focadas nas decisões de planeamento estratégico e tático sob incerteza, considerando complexas interações com níveis mais baixos de decisões operacionais. Espera-se que estas abordagens contribuam para um processo de tomada de decisão mais informado, com o objetivo de: i) maximizar o lucro das empresas; ii) minimizar futuras mudanças no processo de produção; e iv) melhorar a eficiência dos processos, particularmente em relação à utilização de recursos e gestão de resíduos.

Abstract

In recent years the business context in which process industry runs has dramatically changed, becoming operationally more challenging and competitive. In the particular case of the pharmaceutical industry, the decrease of effective patents life and the subsequent increase of generic drugs competition have forced, both industry practitioners and researchers, to pursue new development and manufacturing strategies. Not only the time-to-market has become a key issue, but also sustainability aspects concerning the efficient utilization of the available resources and waste management have driven the development of more innovative optimization-based approaches to achieve operational excellence.

To be responsive and competitive, new strategies must couple decisions made during the drug development cycle with manufacturing decisions. These approaches require integrated decision-making from long to short-term perspectives, where complex problems comprising multiple hierarchical levels, covering dependent time and spatial scales, need to be addressed. Here, well established optimization methods, solely focused on planning and scheduling problems, are no longer suitable, since they do not really consider the uncertainties and risks associated with the interdependency between decisions and they ignore the sustainability and flexibility requirements of the business context. Although important contributions have already been presented addressing multi-level integration in decision-making, to the best of our knowledge, an effective modeling solution still remain as an important open challenge. To significantly improve the overall systems' performance, coordinated and cross-functional holistic approaches must be considered. In this way, globally optimized solutions, that will effectively support the business strategy will be achieved.

This research aims at filling this gap by understanding the industry's operational weaknesses and by further exploring the real value and impact of integrated decision-making, considering aspects such as the fluctuating demand and product variety, the uncertainty associated to each decision level, or some relevant sustainability issues.

The main goal of this research is to develop optimization-based approaches focused on the strategic and tactical planning decisions under uncertainty, considering complex trade-offs and interactions with lower levels of operational decisions. This approach is expected to contribute to a more informed decision-making process and aims at: i) maximizing the profit of the companies; ii) minimizing unnecessary capital investments; iii) minimizing future changes in the production process; and (iv) improving processes efficiency, particularly regarding to resource utilization and waste management.

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1. Introduction

In this chapter the main motivation and objectives of this research will be described. The scope of the study and the research questions will be defined, in order to clearly outline the problem being addressed and give guidelines for a sound development of this work.
The research structure and methods will be also presented as well as the overall thesis outline.

1.1. Motivation and research objectives

Healthcare is one of today's most valuable social and economic assets, laying the foundations for a sustainable and economically developed society. Having a sustainable access to quality healthcare services, although being a complex task, is a main global priority as highlighted in the health policy framework for Europe *Health2020* (WHO, 2013). Regional governments and policy makers have the main responsibility in this task by providing the necessary resources to enable a sound and fair healthcare system.

In this context, the research-based pharmaceutical industry stands at the core of any country's healthcare system, by providing high quality medical drugs and treatments, responsible for preventing, treating, and curing diseases, in an attempt to improve or maintain people's health. Along with these direct benefits for the populations, medicines also contribute to significant cost reductions in the overall healthcare systems, by reducing the need for expensive surgeries and/or long-term care in hospitals. Considering that healthcare spending is continuously growing in the OECD countries (OECD, 2017), the pharmaceutical sector plays a fundamental role in offsetting the medical costs incurred by governments (Pfizer, 2014). Representing on average only about 16% of the global health expenditure across the OECD countries in 2015 (OECD, 2017), some studies (see Afendulis et al. (2011); Congressional Budget Office (2012); IFPMA (2015)) suggest that for every dollar spent on prescription drugs in the United States, a saving of more than two dollars is expected in hospitalization costs (IFPMA, 2015).

Due to this pivotal role in supporting the healthcare structures, and its direct impact on population's well-being, the pharmaceutical industry has been under great pressure to enhance responsiveness, foster affordability, and provide generalized access to high quality medicines. As world economies evolve, it is expected to have more sustainable and reliable healthcare systems and an increased demand for innovative medical drugs with demonstrated therapeutic value.

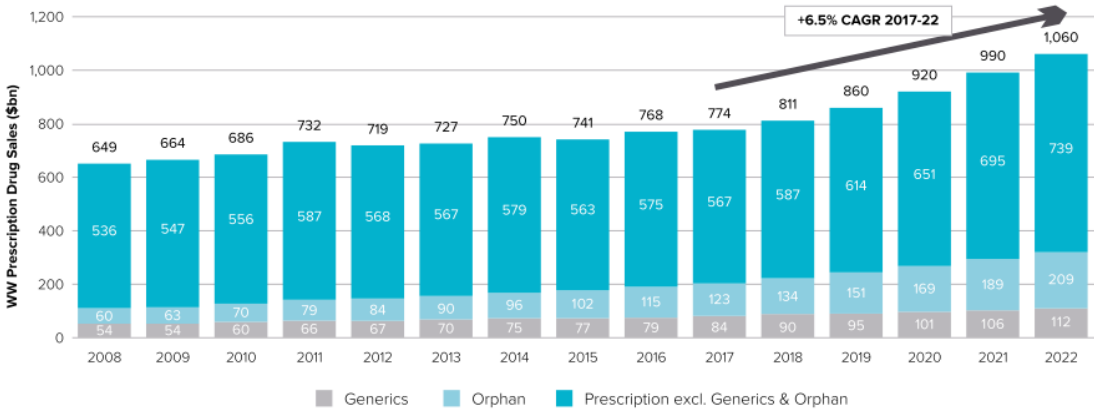


Figure 1.1 Worldwide total prescription drug sales (2008-2022) (Pharma, 2017).

According to Pharma (2017), the worldwide prescription drug sales is expected to grow at a 6.5% CAGR (Compound Annual Growth Rate) in the period 2017-22 (Figure 1.1). This trend of growth also anticipates a more global and competitive marketplace, tendentially more difficult to manage by the pharmaceutical companies.

In this way, as the market becomes increasingly dynamic and competitive, management challenges related to the production, distribution, and delivery of medical drugs, also become more critical and complex.

However, being a highly regulated sector, the pharma business model and its operations have remained relatively unchanged and highly inefficient over decades, having some of the poorest supply chain performance metrics (Shah, 2004; Kaitin, 2010; Yu, 2016). With long development cycles, and high R&D investments with very low success rates, the time-to-market is pointed as the most critical driver in this industry (Shah, 2004). Additionally, considering its high dependence on patent effective life to recover investments, companies are now, more than ever, under great pressure to deliver medical products faster and more efficiently.

In that sense, operational performance that was somehow neglected for decades, has been gaining an increasing relevance in recent years, and operational efficiency is starting to emerge as a key differentiation factor in this sector. Therefore, chemical-pharmaceutical companies are now starting to move from their traditional business model almost exclusively dedicated to product innovation, to a more cost-efficient operating mode (Kaitin, 2010; Gautam & Pan, 2016).

This transition, however, is still at its infancy of development, companies having to face some major management challenges yet to overcome. Namely, the high complexity of the current pharmaceutical supply chain, the lack of coordination between operational functions, the declining R&D productivity, the need for effective production/capacity planning and asset utilization, and the ability to efficiently align the goals of different decision-levels.

In this regard, decision-making tools can play a key role in supporting this transition process. Being inherently associated with operational performance indicators, they aim to support business and improve operational decisions. Thus, the development of new decision support tools incorporating the unique complexities of the pharmaceutical industry is, therefore, crucial and urgent, to overcome these challenges, and to achieve the required levels of efficiency to sustain competitiveness.

In this context, Process Systems Engineering (PSE) and Operations Research (OR) communities have been developing reliable decision tools in the past years based on analytical systems such as simulation, optimization, and hybrid simulation-optimization based approaches, covering a broad diversity of problems (Kallrath, 2002; Shah, 2004; Floudas & Lin, 2005; Verderame et al., 2010; Laínez et al., 2012; Moniz et al., 2015c; Grossmann et al., 2016b; Reklaitis, 2017). However, well established enterprise-wide optimization applications, such as those developed for planning and scheduling, exhibit important limitations in accurately capturing some relevant dynamics of the real supply chain behaviour (Naraharisetti et al., 2009; Dias & Ierapetritou, 2017). Typically, these models

seldom consider the plethora of factors and external disturbances affecting the business and its strategy within a sustainable and flexible supply chain context. For instance, the variety of decisions spanning across different hierarchical levels and business functions are typically considered individually, and their interactions and coordination are poorly understood and often neglected.

Moreover, some of the available tools are highly complex to understand and implement within a real organization, where business responsiveness asks for simpler and more intuitive models in which the decision-maker's participation is not only a valuable insight, but also a paramount building component of the decision-making process.

Therefore, this research work aims at meeting the pharmaceutical industry main challenges, in their path for enhanced operational efficiency by understanding their main operational fragilities in the current business context, and by developing effective solution approaches for (strategic and tactical) planning during the new product development (NPD) phase. In this way, it aims at addressing four main research goals (RG):

- *RG 1.* mapping the current state of the pharmaceutical business and production context and their decision-making processes;
- *RG 2.* understanding the current market dynamics and the expected business evolution, as a basis for developing a generalized reference framework for the most relevant decision problems arising from the complexities of the new pharma paradigm;
- *RG 3.* developing optimization-based approaches to enhance the integrated strategic and tactical planning decisions under uncertainty, and to improve the overall operational efficiency;
- *RG 4.* incorporating the decision-maker risk-attitude in the characterisation of strategic decisions.

The joint development and successful accomplishment of these four research goals will have a positive operational impact in the chemical-pharmaceutical industry, by achieving the following expected outcomes (O):

- *O1.* a comprehensive decision-making reference framework to provide a structured support to academic researchers and industrial practitioners in systematizing their problems, while taking into account all the relevant factors affecting future supply chain operations.
- *O2.* a unified decision support tool to address the stochastic product launch planning problem in the pharmaceutical industry, which includes:
  - *O2.1.* a simulation-optimization based approach to improve overall operational efficiency, by integrating process design and production planning decisions under a highly uncertain environment;
  - *O2.2* a multi-objective approach, explicitly considering the decision-maker preferences, to determine the strategic design solutions that improve the productivity level during product development.

1.2. Scope of analysis and research questions

According to the research goals defined in the previous section, two different levels of analysis are considered. On one hand, regarding the first two research goals (RG 1 and RG 2), the work is centred on the pharmaceutical business and production context and its SC operations. Specifically addressing the related decision-making processes as the main unit of analysis, this thesis is focused on their conceptual characterization and respective future challenges.

On the other hand, to meet the last two research goals (RG 3 and RG 4), this study is concentrated on the new product development (NPD) process, as this is the most critical and challenging stage in the pharmaceutical product lifecycle. The work specifically addresses the operations during the clinical trials activities and their planning challenges. Here, the traditional multipurpose batch manufacturing system is the main unit of analysis, focusing on the stochastic product launch planning problem, including integrated process design and production planning decisions for the clinical trials. Figure 1.2 schematically represents the scope of the research work within the context of the pharmaceutical product lifecycle.

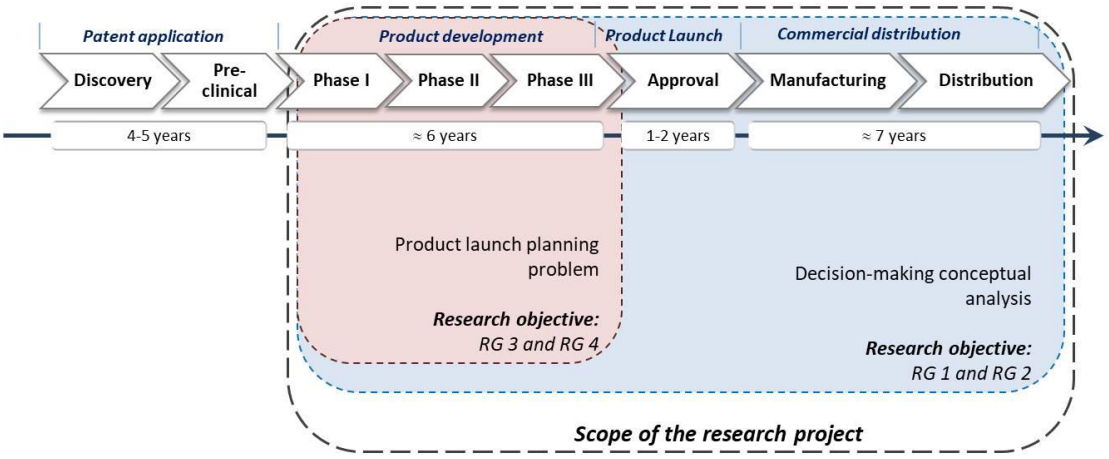


Figure 1.2 Pharmaceutical product lifecycle and scope of the research project.

Considering this, three research questions were formulated to guide a sound development of the research and meet the defined objectives. The questions are expressed as follows:

RQ 1: *How is recent research contributing to overcome the current challenges in chemical-pharmaceutical operations management?*

RQ 2: *What should be the main building blocks of a useful chemical-pharmaceutical industry's decision-making framework?*

RQ 3: *How can pharmaceutical companies enhance their strategic and tactical decision-making processes through optimization-based approaches, during product launch planning and considering its unique complexities and uncertainty environment?*

The first research question aims, firstly, to leverage the understanding regarding the current developments in the pharmaceutical supply chain management and, secondly, to better comprehend how these developments have impacted the industry in what concerns its operational efficiency, and what are the main unmet challenges.

The second research question aims at guiding this research work in developing a new decision-making reference model capable of accommodating the expected future operating practices and business models. The main objective is to clearly identify the main building blocks and respective interactions, so as to support the development of future decision-making tools. Following this, the third research question focus on the development of an efficient optimization-based decision-making tool for strategic and tactical planning, by providing guidance regarding what should be the main components and strategies for dealing with the main challenges and complexities of this industry.

1.3. Research Structure and Methods

Based on the above considerations, the research work is structured around two stages. The first stage is dedicated to a conceptual analysis of the pharmaceutical "*Business Context*" and its market context as a whole, while the second is focused on the "*SC Operations*" specifically addressing the strategic and tactical production planning decisions during the NPD process. A schematic representation of the research structure and methods followed in this work is shown in Figure 1.3.

First, the conceptual analysis, designed to answer RQ1 and RQ2, was performed based on an empirical study supported by a thorough literature review and a survey of market reports. From this analysis, the prevailing current pharmaceutical business strategies and supply chain operations principles are outlined, as perceived by both, practitioners and researchers. Following this, the expected new pharmaceutical paradigm is anticipated as well as its impact on the supply chain operations and related decision-making processes.

The following stage in the work aims at answering RQ3, and is focused on the operations planning during the NPD process. In this case, the work includes techniques such as Mixed Integer Linear Programming (MILP) and Multi-Objective Integer Programming (MOIP) models, for the determination of process design (strategic) and production planning (tactical) decisions. To deal with uncertainty, Monte Carlo Simulation (MCS) approaches are applied.

The models were validated using a small industrial case, based on a typical contract manufacturing organization (CMO) for Active Pharmaceutical Ingredient (API) production. The problem instances

were created with values estimated from the literature and validated by comparing those values with the current industrial practice.

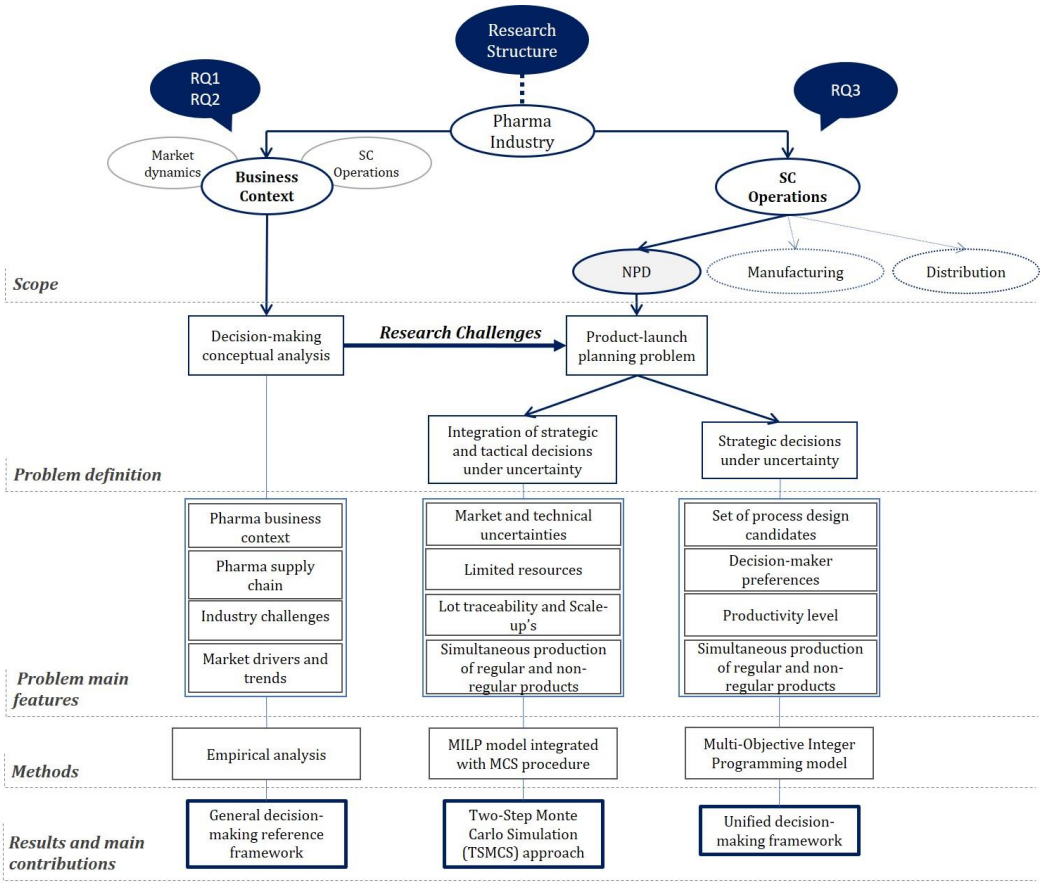


Figure 1.3 Research structure and methods.

1.4. Thesis Outline

The present thesis is organized following the main research structure presented above and depicted in Figure 1.4.

Therefore, in chapter 2, a thorough conceptual analysis is performed in order to portray the current state of the industry and their planning decision-making processes. The main research challenges and opportunities for improvement are identified, as well as the current market dynamics, in the form of drivers and trends, in order to evaluate their impacts on the global supply chain and envision future operations and planning decision-making processes. A general decision-making reference framework is then proposed, to provide support and guidance in the decision-making processes, taking into account all the complexities associated to the new pharmaceutical paradigm.

In chapter 3, the stochastic product launch planning problem is presented, with a description of its main features, challenges, and relevance for the pharmaceutical industry.

A novel approach, combining a MILP model and a Monte Carlo Simulation framework is proposed, to efficiently tackle the integrated process design and production planning decisions, under uncertainty in product demand and clinical trials outcomes. The main goal of the developed approach is two-fold: to assess the impact of several sources of uncertainty on long-term decision-making during the NPD process; and to provide a large-range analysis of the uncertainty parameters, by mapping the most likely alternative decisions, and thus enabling earlier and better decision-making

Chapter 4, presents, an extension of the previous model to determine the unique strategic decisions under uncertainty. A Multi-objective Integer Programming model, embedded in a unified decision-making framework, is developed to obtain the final design strategy that "maximizes" productivity, while considering the decision-maker preferences. The model is solved by the weighted-sum method, and an approximation of the Pareto efficient frontier is determined. In this case, the purpose is to determine the unique strategic solution, by balancing the investment costs to develop a new drug and the production capacity allocation to accommodate the uncertain future needs.

Finally, chapter 5 concludes and summarizes the research work developed in this thesis, highlighting its main contributions and presenting some recommendations for future research.

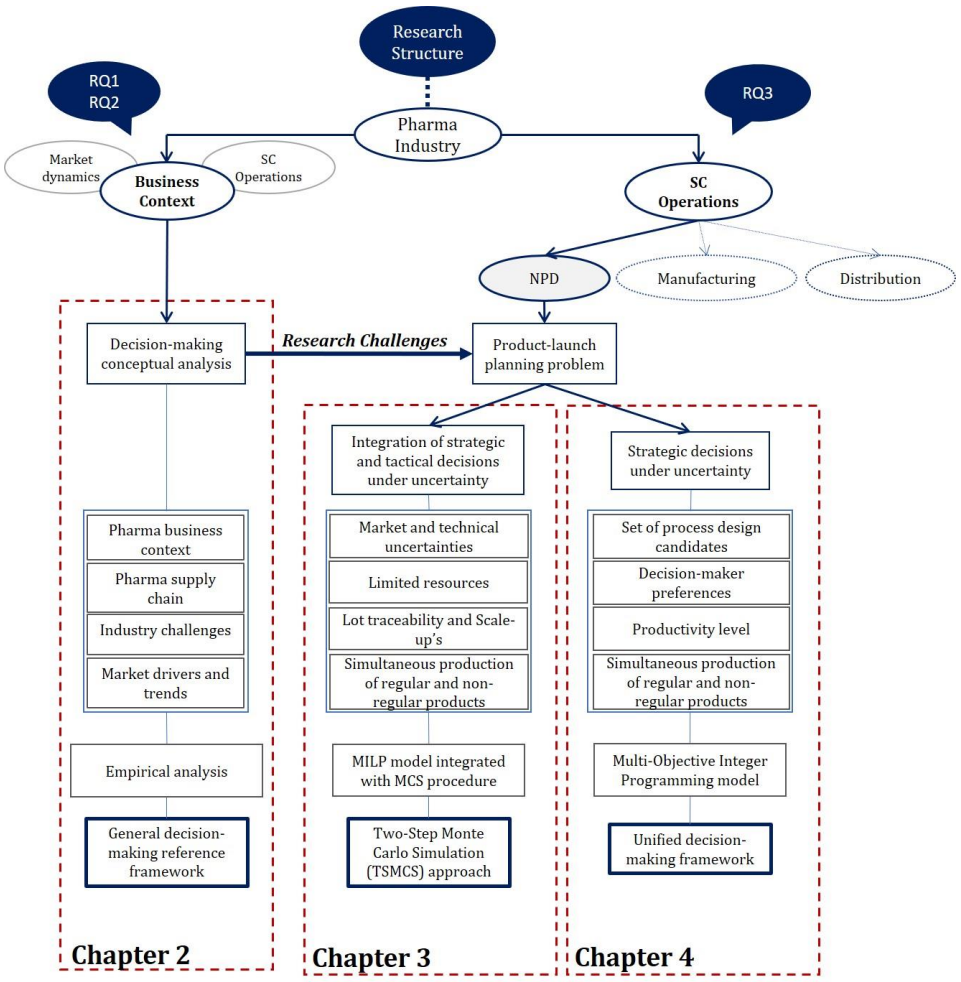


Figure 1.4 Thesis outline.

1.5. Publications

The research developed in this doctoral project is supported by several papers that were already published or are under review, in international peer reviewed journals. Each chapter is directly related to a specific individual publication, as presented below (this may have resulted in some, hopefully minor overlapping throughout the different chapters).

***Chapter 2*:**

Marques, C. M., Moniz, S., de Sousa, J. P., Barbosa-Póvoa, A. P., & Reklaitis, G. (2019). Decision-making in the chemical-pharmaceutical industry: findings and future research directions. *Working paper to be submitted for publication to an international journal.*

Chapter 3:

Marques, C. M., Moniz, S., de Sousa, J. P., & Barbosa-Póvoa, A. P. (2017). A simulation-optimization approach to integrate process design and planning decisions under technical and market uncertainties: A case from the chemical-pharmaceutical industry. Computers & Chemical Engineering, 106, 796-813.

Chapter 4:

Marques, C. M., Moniz, S., & de Sousa, J. P. (2018). Strategic decision-making in the pharmaceutical industry: A unified decision-making framework. Computers & Chemical Engineering, 119, 171-189.

Conference Proceedings

Marques, C. M., Moniz, S., de Sousa, J. P., & Barbosa-Póvoa, A. P. (2016). Optimization and Monte Carlo Simulation for Product Launch Planning under Uncertainty. In K. Zdravko & B. Miloš (Eds.), Computer Aided Chemical Engineering (Vol. Volume 38, pp. 421-426): Elsevier.

Marques, C. M., Moniz, S., de Sousa, J. P., & Barbosa-Póvoa, A. P. (2017). A simulation-optimization approach to integrate process design and planning decisions under technical and market uncertainties. In Foundations of Computer Aided Process Operations / Chemical Process Control. Tucson, Arizona.

2. Planning decision-making in the chemical-pharmaceutical industry

In this chapter a comprehensive analysis of the current state of the industry and its planning decision-making processes is performed and a new general decision-making reference framework is proposed to comply with the today's business context.

The content of this chapter is based on the working paper currently being prepared for submission to a peer reviewed international journal.

Abstract

The chemical-pharmaceutical business context is facing an unprecedented fast-changing environment, with new market and technological trends significantly impacting the companies' operational strategies. Managing the pharmaceutical supply chain (PSC) operations is, therefore, ever more complex and challenging, requiring a multi-perspective approach.

This work intents to address these issues by, first, presenting a comprehensive overview of the current state of the industry and research developments, in order to recognise the current and the forthcoming decision problems; and, then, by developing a reference framework to provide support and guidelines to structure the production systems. This will be achieved through a multi-perspective analysis that encompasses strategic and tactical planning decision-making, in the new business context of the chemical-pharmaceutical industry. Interesting findings reveal a lack of research addressing the most prominent trends currently driving the industry, such as the patient centricity or the new technological interventions. This may be an important indicator of the disruptive nature of these expected changes in a highly conservative industry. This work reveals the main market drivers and trends that are putting pressure on the industry, as well as the main resulting research challenges. The contributions of this work are twofold. First, the main building blocks of the expected new operational paradigm are outlined together with their impact on the PSC management. Second, a new decision-making reference framework is proposed to assist the development of optimization-based models.

2.1. Introduction

The chemical industry sector is a broad area of the process industry, representing alone (without considering pharmaceuticals, food and drink, and pulp and paper) approximately 7% of EU industrial production, and 1.1% of EU GDP (EC, 2018).

Similarly to other industries (such as discrete manufacturing), the typical supply chain in the chemical industry includes several entities embedded in a coordinated network, such as: primary and secondary manufacturers, suppliers, warehouses, distributors, and customers. Nevertheless, in this sector products present some specific features that are not negligible and usually have relevant impacts on the supply chain operations and consequently on the decision-making processes. Some of those features include: (i) the non-discrete nature of the final products, making it difficult to present them as individual and countable units; (ii) impossibility to disassemble the final product into their original raw materials, and (iii) huge variety of non-discrete and immiscible materials with their own unique characteristics (Naraharisetti et al., 2009). On the other hand, the process plant is

composed of a network of units performing various physicochemical operations frequently in batch and multi-product/multipurpose operating modes, leading to high flexibility, but also to very low material and capital equipment efficiencies (Shah, 2005; Naraharisetti et al., 2009). In addition to that, the need for rigorous and expensive cleaning and sterilization operations, as well as maintenance procedures, results in long and undesirable lead times (Naraharisetti et al. (2009), Shah (2005)). According to Shah (2005), only 0.3-5% of the supply chain cycle time (considered as the time between material entering as raw material and leaving as product) involve value-adding operations. In that sense, it became clear that there is a great room for improvement and efficiency enhancement in chemical industry supply chains. Other key issues, such as the high sensitivity to energy prices, environmental and safety regulations, clearly distinguishes this sector from other supply chains (Naraharisetti et al., 2009).

Depending on the characteristics of their final products, the chemical industry is usually grouped into different sub-sectors or classes. According to Smith (2005) three major classes can be distinguished: bulk chemicals; fine chemicals, and specialty chemicals. Each of these classes has different added values to the final product and intrinsic characteristics that influence the representation of the production process and consequently the focus of the main management decisions (Smith (2005), Srinivasan et al. (2006)). Bulk chemicals are mainly characterized by their undifferentiated character and large-scale production. In this case the selling price is the main purchasing driver, and for that reason margins tend to be slimmer in order to be competitive. On the other hand, fine chemicals are produced in a small scale, and represent high purity products mainly used as intermediaries in other industries. Nevertheless, this class of products also presents a strong undifferentiated nature (despite some differences that can arise regarding the purity grade between different manufacturers), making, once again, selling price as the main driver. Finally, regarding specialty chemicals (such as pharmaceuticals, cosmetics, flavourings, and others), these can be highly differentiated products, that tend to be purchased based on their function / perceived value, rather than price or chemical composition. Furthermore, being highly knowledge-intensive, intellectual property plays a critical role in this sector. In that sense, production tends to be in small volumes, but with very large margins. The characteristics associated with each of those classes tend to be determinant on the main decisions related to supply chain management and production efficiency (see Figure 2.1). This has been true for many years, with the individual key challenges being confined to the specific industry classes. However, the fast-changing business context experienced in the last decades is also shaping the changes occurring in the industry operating mode, bringing new paradigms to light. This is particularly the case of the pharmaceutical industry, in which significant market and business changes have been observed in recent years, with major impacts on the sustainability of this industry. Pharmaceuticals are part of the specialty chemicals in which both, product and process development, need to follow rigid frameworks imposed by regulatory agencies such as the FDA (Food and Drug Administration) in USA, and the EMA (European Medicines Agency) in Europe (Smith, 2005). Therefore, pharmaceutical companies are now being forced to overcome the barriers that define the specialty chemicals and incorporate a transverse view of the whole

chemical industry (Figure 2.1). In that sense, the main concerns traditionally associated to the bulk and fine chemical classes, such as cost reduction and production efficiency, are now also major concerns in the pharmaceutical industry which has been highly inefficient.

According to some authors (Singh et al., 2016) pharmaceutical companies can benefit greatly by learning not only from the operational efficiency of the bulk chemical industry, but also from other industrial sectors (automotive, electronics, etc).

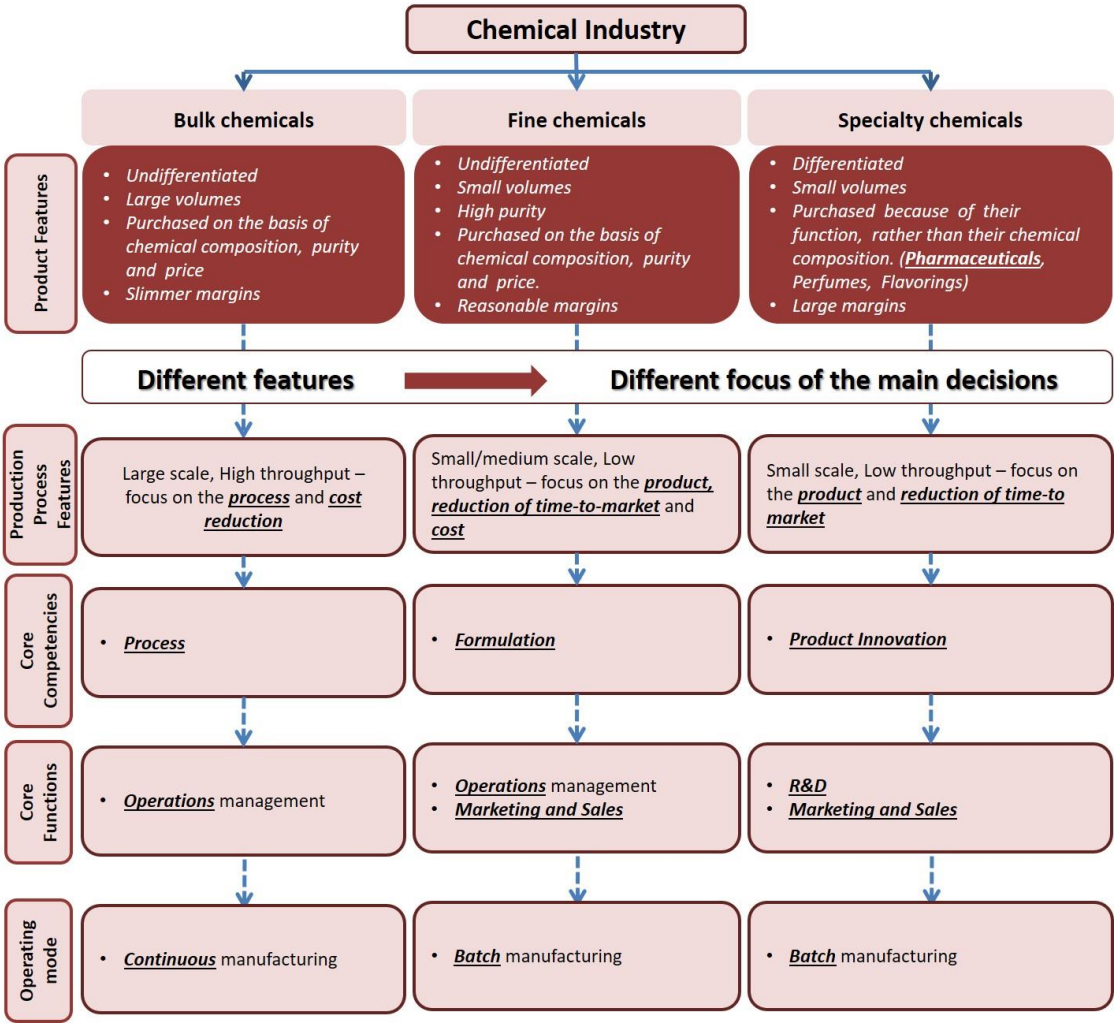


Figure 2.1 Key differences between the three main classes of the chemical industry.

Additionally, new trends are also being observed in recent years across the whole process industry, encouraging a shift from a cost-driven development to a sustainable-driven development (Heintz et al., 2014). Not only economic goals, but also environmental, safety, and social aspects should be simultaneously considered in supply chain management decision-making (Barbosa-Póvoa, 2012; Barbosa-Povoa & Pinto, 2018) Over the last years, an important body of research work has been published focusing on various sustainability aspects in the process industry, as highlighted in some important surveys (Srivastava, 2007; Barbosa-Póvoa, 2009; Nikolopoulou & Ierapetritou, 2012b; Eskandarpour et al., 2015; Garcia & You, 2015; Barbosa-Póvoa et al., 2018). The chemical industry (including the pharmaceutical sector) plays a critical role in this regard, as its operations are strongly

dependent on resources and utilities such as energy and water, thus having a significant environmental and social impact.

Technological breakthroughs, such as continuous manufacturing (Lee et al., 2015) and the advent of Industry 4.0 (Branke et al., 2016), are already shaping and transforming the traditional pharmaceutical manufacturing landscape.

The emergence of new markets and new healthcare systems is also expected to have a significant impact on the pharmaceutical supply chain operations and business models.

This highly dynamic context that is already in place is putting pressure on pharmaceutical companies to leave their traditional operating strategies and move forward to the path of higher levels of efficiency, sustainability, agility and customer value creation.

Accordingly, it is clear that supply chain management in the pharmaceutical industry has become a very complex challenge, with an amalgam of new possible decision-making problems that interact in a complex network of agents and their relations, that are not always obvious or easy to understand (Varma et al., 2007). Thus, despite the increased effort made by researchers in adopting an ever more global and integrated vision of the pharmaceutical supply chain, research works found in the literature are still very fragmented in what concerns the enterprise-wide optimization paradigm, and are strongly limited to the traditional operating strategies (Grossmann, 2005; Laínez et al., 2012).

Moreover, existent taxonomies and frameworks used to classify the decision problems in the context of pharmaceutical industry need to be adapted to the current situation. Thus, it becomes clear that a new general reference framework, covering the main operations planning problems that arise from this new context, is key in this field and brings benefits for both academia and industrial practitioners.

The main goal of this chapter is then twofold. First, it aims at presenting a comprehensive overview of the developments made so far to grasp the main operations planning problems in the pharmaceutical industry and to bring to light the forthcoming new challenges. Second, it proposes a reference model to establish a roadmap for the planning decision-making process in this industry, accounting for the new challenges imposed by the current business and technological context.

2.1.1. Methodology

To establish the basis for understanding today's pharmaceutical context and its strategical and tactical planning challenges, a comprehensive analysis is performed following a sequence of three steps outlined in Figure 2.2. These include: i) pharma context analysis; ii) opportunities for change; and iii) new pharma paradigm.

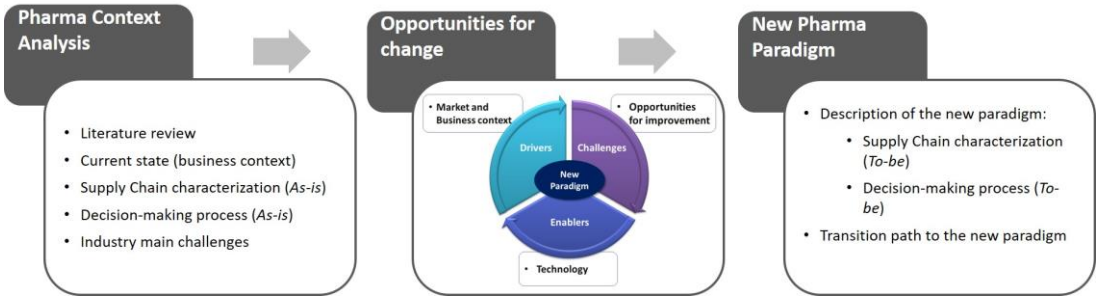


Figure 2.2 Main steps adopted.

The first step consists in a conceptual analysis of the current state of the pharmaceutical industry operations and business context, as it is perceived by both, practitioners and researchers. The main supply chain operational performance indicators are outlined, as well as the corresponding decision-making processes, showing the industry main weaknesses and opportunities for improvement. Additionally, a thorough literature review is performed to assess how the academic community is addressing the different pharmaceutical supply chain challenges and identifying the most prevalent research gaps.

The second step (opportunities for change) consists in understanding the market dynamics and the technological context behind the main driving forces and enablers, that are currently pressing the industry and driving the companies to pursue an unprecedent mind-set change.

A combined analysis of all the three components – challenges, drivers, and enablers – will provide insights regarding the path towards a new operational supply chain and associated decision-making processes.

Finally, in the last step, the main components of the foreseen new pharma paradigm will be identified, as a way to enable the definition of the new supply chain operational model as well as the characterization of the new planning decisions. The integration of these components will lead to a general decision-making reference framework.

2.2. Analysis of the pharmaceutical industry context

The pharmaceutical industry is a key asset of the European economy: it is one of Europe's major high-technology industrial employers and generates about three to four times more employment indirectly (EFPIA, 2016). It plays a critical role in the healthcare structure of each country by providing medicines and vaccines with direct impact on population's quality of life. Along with the direct benefits for the population, medicines also contribute to significant cost reductions in the expenses of the global healthcare system of each country, by reducing the need for expensive surgery and/or long term care in hospitals (Pfizer, 2014). This is very significant and highlights the economic

importance of this industry for a country, as it is a key player in guaranteeing the economical sustainability of any healthcare system.

The pharmaceutical industry sector is mainly composed by large R&D multinationals, local companies, generic manufacturers, contract manufacturing organizations (CMO) – without their own product portfolio, and biotechnological companies mainly focused on research and drug discovery (Sousa et al. (2011), Shah (2004)). While the large R&D based multinationals represent by far the most economically important sub-sector in terms of sales, generic manufacturers are responsible for supplying the vast majority of medicines distributed worldwide in terms of volume. Therefore, despite many of the stakeholders involved being the same, their supply chains and drivers (specially financial) are significantly different (Association for Accessible Medicines, 2019). In the generic drugs' case, supply chains are mainly characterized by large portfolios of finished products and distribution chains, without the highly risky intellectual research and product development activities. On the other hand, the R&D based multinationals cover the entire product life-cycle, since discovery to commercial distribution, relying largely on a careful balance between the products being off-patent and the launch of new drugs under patent protection. Thus, in this case, the supply chains tend to be much more complex and difficult to manage, and therefore, also more vulnerable to uncertainty and risk. Considering these aspects, this chapter will be mostly focused on the analysis of this particular sector.

Similarly to other products, the general life-cycle of a pharmaceutical product starts with product development, followed by market launch of the successful products, a growth phase in sales, a maturity phase and finally it reaches the end of life with a decline phase (Figure 2.3) (Laínez et al., 2012).

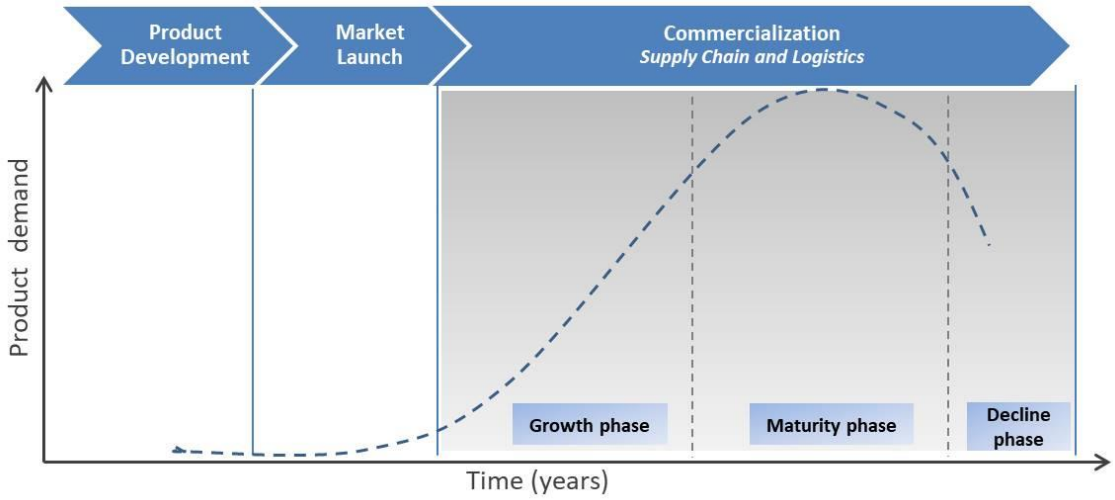


Figure 2.3 Pharmaceutical product life-cycle (adapted from (Laínez et al., 2012)).

However, in the pharmaceutical industry, each of these stages has some specific features, that are different from other industries, and that create some significant and unique management challenges. In order to better understand these challenges, three main sub-topics are proposed here as the most

relevant in these supply chains, regarding their strategic and tactical planning problems and decision-making processes. These topics are: i) product development and market launch, due to their fundamental role in product innovation and in the economic sustainability of pharmaceutical companies; ii) supply chain and logistics, which are typically global, with complex drug delivery systems that are difficult to manage; and iii) decision-making challenges, emerging from planning problems that have been addressed in this industry and how they have been handled.

With this classification scheme, we attempt to capture the major problems, trends and challenges, in the strategic and tactical process planning optimization.

2.2.1. Product development and market launch in the pharmaceutical industry

In the innovative product sector of the pharmaceutical industry the product development phase is particularly challenging essentially due to the well-known high expenditures, low success rates, and long development cycles.

Typically, a new product development (NPD) phase involves four main activities: *discovery*, *pre-clinical tests*, *clinical trials* on humans, and *approval and product launch* (including pharmacovigilance after launch). The time laps between discovery and market launch can take an average of 15 years (Federsel (2009), Laínez et al. (2012)) with a total cost per approved new compound of $ 2,558 million in 2013 dollars, as recently estimated by DiMasi et al. (2016) and indicating an increase from the authors previous estimates. Also, in the recent outlook report (Pharma, 2017) the total R&D spending is expected to reach US$181 billion in 2022, corresponding to a grow at a rate of 2.4% per year. The allocation of this investment cost in product development is outlined in Figure 2.4, with clinical trials alone representing almost 50% of the total investment (EFPIA, 2016).

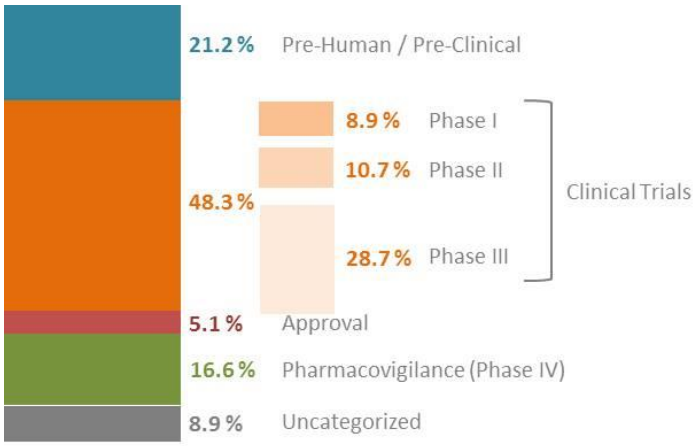


Figure 2.4 Allocation of R&D investment by main activity (EFPIA, 2016).

In the *discovery* activities thousands of chemical compounds are tested until a promising new molecule (Active Pharmaceutical Ingredient – API) is found. The new API is then subjected to extensive tests (*pre-clinical tests*) conducted in animals to determine the toxicity and safety levels for human testing in the following *clinical trials* stage. Clinical trials are not only the most expensive

activity during product development (see Figure 2.4), but also the most time consuming, taking about 5 to 6 years to complete all the three consecutive phases (I, II, and III) (Colvin & Maravelias, 2008). Each of these phases requires an increased amount of the new drug to perform the set of rigorous tests imposed by the regulatory agencies. In phase I, the new molecule is tested in humans for the first time, mainly for safety and dosage determination. In phase II, tests are performed on a medium scale for efficacy assessment, and finally, in phase III, tests are conducted on a large-scale to compare the performance of the new therapeutic compound with other existing treatments, and assess its long-term effects (Colvin & Maravelias (2008), Varma et al. (2008a), Levis & Papageorgiou (2004)). Only after successful completion of all the clinical trials phases a New Drug Application (NDA) is submitted for approval and market launch. According to DiMasi et al. (2016), the overall probability of a new drug that enters clinical trials to be approved was estimated to be 11.83% compared to 21.50% estimated by the same authors in previous studies. Thus, not only the investment in R&D is increasing, but also the success rates in clinical development are decreasing (Bunnage, 2011; Pammolli et al., 2011b; Wang et al., 2015).

Additionally, after a new drug is commercially launched, market success is not guaranteed. This may happen due to the lack of differentiation or perceived therapeutic value not only by the end-users, but particularly by the healthcare payers, who are more concerned with the cost/benefit impact of the new drug on their patient population, when compared to existing treatments.

Simultaneously with the product development described above, many other activities related to the production process need also to be undertaken, since not only the product, but also the production process needs to be approved by the regulatory agencies. Furthermore, in order to assure availability of commercial scale production capacity as soon as the new drug is approved, the investment in new production facilities for the API production should be made around 5 years before market launch (Stonebraker, 2002; Hansen & Grunow, 2015a), and this is well before the completion of clinical trials and FDA approval is known. These decisions, although highly risky, are essential to prevent delays in the market launch, and consequent revenue losses resulted from the reduction of the patent effective life.

Finally, after regulatory approval of both product and process, the new drug is *launched* under patent protection into the market, through a network of manufacturing and distribution agents embedded in a coordinated supply chain Figure 2.3.

Overall, the product development process in the pharmaceutical industry is still highly inefficient, with very low levels of productivity, making it a fruitful area for improvement (Paul et al., 2010a; Pammolli et al., 2011b). The main challenges that pharmaceutical companies are facing today can be summarized in three major categories:

1. minimize the development lead time (reduced time-to-market);

2. maximize the product pipeline value, by guaranteeing a good balance between the number of products in the pipeline and their technical quality (safety, efficacy, and market differentiation);

3. minimize development costs.

2.2.2. Pharmaceutical industry supply chain and logistics

After the market launch, the process enters a growth phase in which companies try to capture and establish a market share as large as possible. As innovators, companies usually witness a sustainable growth in sales in a relatively easy way, while also trying to build customer confidence, until they reach the maturity phase (Figure 2.3).

Although the maturity phase can provide the highest returns from the product, this phase is particularly challenging for the innovator manufacturers. As the drug patent life approaches the end, generic manufacturers become active in preparing their prompt entry immediately after the expiration date. Usually, the first generics enter the market with prices as low as 25% of the original brand. These prices continue to decline over time as new generics also enter the market, competing with each other solely by price (Petrova, 2014). This factor introduces new dynamics in the supply chains of both innovators and generic drugs manufacturers. While in the first case the original brand starts losing market share relatively fast without a significant decrease in price, in the second case the drug price drops considerably, but with an important growth in volume and market share.

According to Petrova (2014), in the USA, approximately 74% of all new (brand) drug sales occurs in the exclusivity period after drug approval. In this way, companies should be able to ensure adequate production and capacity management, as well as effective supply distribution in order to be responsive and sustain the required service levels during this short time window.

This is a challenging endeavour given that the pharmaceutical industry is inherently global, and consequently supply chains are usually large and complex, comprising a network of product (primary and secondary) manufacturers, packaging facilities, regional distribution centres (wholesalers), and final healthcare providers such as hospitals, pharmacies, etc. Due to globalization and Mergers and Acquisitions (M&A) strategies, all these agents (including the product manufacturers) can be in several different locations around the world, forcing companies to deal with different regional policies, cultures and taxes structures. Adding to this already complex network (raw material suppliers, contract manufacturers, and third-party logistics providers), a high level of coordination is required between all these agents, government bodies, and regulators. However, each of these agents tends to function independently, pursuing their own operational efficiencies and goals, often with some lack of transparency or visibility. This leads to disconnected systems, with the occurrence of disruptions and inefficiencies that propagate throughout the supply chain network (Privett & Gonsalvez, 2014; Srai et al., 2015b).

At the core of this disconnected system is the pharmaceutical drug manufacturing process, which typically occurs in two autonomous stages – the *primary* and the *secondary* production, adding additional complexity to the SC and significant operational inefficiencies.

The *primary* production consists of the conversion of starting materials into Active Pharmaceutical Ingredients (API). This is performed through several chemical and separation processes that can involve long processing times (Sousa et al., 2011). Usually, the chemical-pharmaceutical plants process low production volumes with high product variability using the still predominant batch and multipurpose operating modes, in which different products are produced by sharing all the available resources (Floudas & Lin, 2004). In batch processes there is a well-defined start-up step, as well as the follow-up and final steps that are defined by product recipes (Kallrath, 2002). This allows a clear identification of the intermediaries and products being produced and ensures lot traceability, a critical aspect in the pharmaceutical industry. Thus, the batch operating mode can lead to higher flexibility and economical savings, due to the spread of capital across multiple products. However, the inherent gain in flexibility is achieved at the price of additional complexity of the production system. This complexity is translated into long changeovers and cleaning tasks required by the "stop-and-start" steps and the regulatory requirements, to provide assurance that there is no possibility of cross contamination between API.

Moreover, since high customer service level is a key focus of this industry, inventories tend to be high to guarantee an acceptable level of responsiveness. Therefore, batch plants for primary production can be the bottleneck of the entire supply chain, being characterized by some poor performance measures, such as (Shah, 2004; Laínez et al., 2012; Singh et al., 2016): (i) long production cycle-times; (ii) lack of responsiveness (inflexibility to sudden changes); (iii) many unproductive tasks (changeovers, Cleaning-in-Place (CIP) and Sterilization-in-Place (SIP)) – contributing to long setup times (in the order of weeks or higher) and also to an increase of energy and water utilization; (iv) high levels of inventory to compensate for slow responsiveness to market dynamics; (v) high levels of expired final product due to the excess of inventory; (vi) inefficient materials utilization mainly due to low production yields; and (vii) low equipment utilization.

Despite the clear great opportunity for operational improvement and production optimization, only recently have industry practitioners and researchers started looking at these issues as critical factors impeding industry sustainability (Laínez et al. (2012), Moniz et al. (2015a)). Continuous manufacturing presents new opportunities in this regard as has already been demonstrated by its successful adoption in several manufacturing sectors such as food & beverage, oil & gas, petrochemicals and polymers (Bieringer et al., 2013; Harrington et al., 2014). In the pharmaceutical industry, however, despite the recent advances in continuous manufacturing capabilities and the increasing awareness of its advantages (Klutz et al., 2015; Rogers & Ierapetritou, 2015; Ierapetritou et al., 2016), as well as the encouragement by regulators such as FDA (Lee et al., 2015), the adoption has fallen far short of the desirable, and the traditional batch operating mode still prevails in the primary manufacturing stage.

On the other hand, *secondary* production is responsible to transform the API, produced in the primary stage, into a suitable form for commercialization. It usually involves further processing of the API and packaging into discrete final products, which are typically presented as solid dosage forms (such as tablets or capsules), semi-solid (such as ointments or gels) or liquid dosage forms (such as injectables) (Gad, 2008). Depending on the specific product characteristics or final dosage form, the (secondary) manufacturing process and its associated distribution network imply different costs and lead to several interesting challenges. These differences are mainly associated to the production of complex solid forms (such as bilayer tablets or extended release formulations) and sterile preparations (such as injectables), requiring more rigorous and expensive manufacturing processes. Moreover, biologics entail significant challenges associated to temperature sensitivity and control, requiring the need for complex and expensive cold chain distributions.

Nevertheless, traditional solid dosage forms are still the most common, representing about 60% of all drug products (Wright, 2015; Ierapetritou et al., 2016), and comparatively less expensive formulations. The associated manufacturing processes are well established, making this stage more responsive and closer to local markets, usually operating on a "pull" basis in contrast with the traditional "push" operating mode that characterizes the primary production stage.

Secondary production is both physically and organisationally separated from primary production and consists of several manufacturers geographically spread and responsible to satisfy local markets (Sousa et al., 2011). Moreover, the construction of additional capacity for secondary production may take only about 3 months, making capacity decisions much more informed and less risky when compared to primary production (Hansen & Grunow, 2015a).

The finished drug products are then shipped to packaging facilities and from these to final consumers mainly through wholesalers that play a critical role in this industry. The current (batch operating mode) pharmaceutical supply chain is depicted in Figure 2.5.

The pharmaceutical supply chain has been inefficient over the years and across its different levels. Companies have been slow to react to market changes, and scale-ups (or scale-downs) are difficult to perform, costly, and ineffective in absorbing the demand dynamic. Also, the functional "silos" (Garnier, 2008; Srai et al., 2015a) over the entire supply chain network hinder an end-to-end visibility leading to operational inefficiencies, and quality and safety concerns. According to Privett & Gonsalvez (2014) the lack of coordination (together with fragmentation and a "silos" based system) is, for industry practitioners, at the top of the main supply chain issues, followed by the inventory management issue.

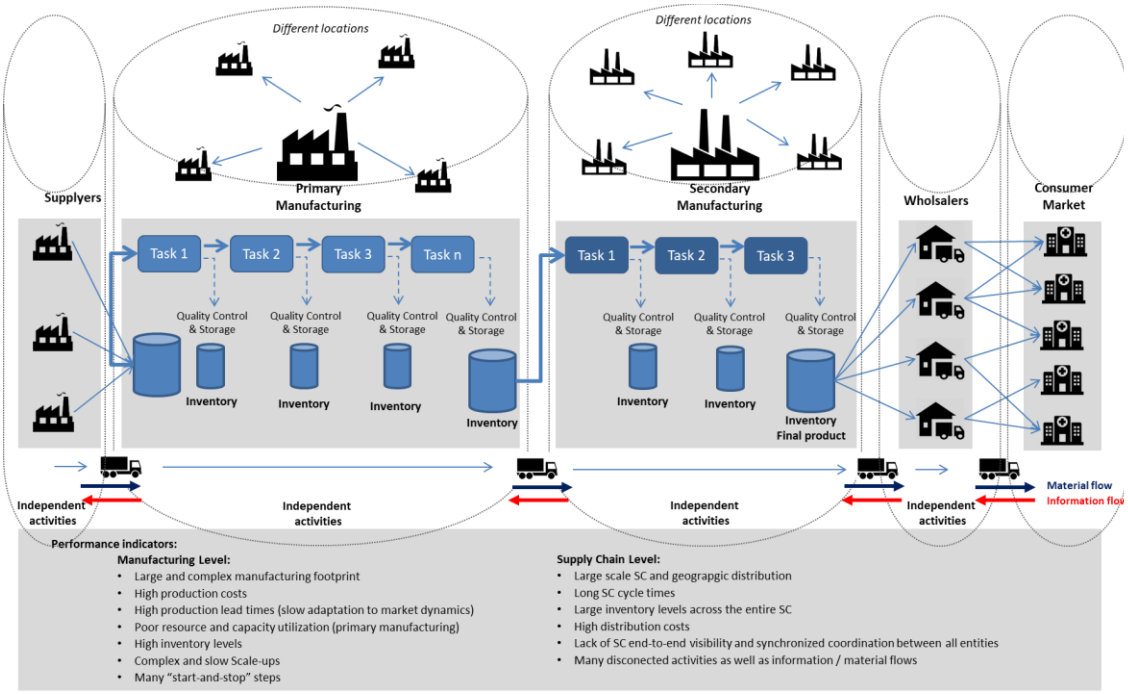


Figure 2.5 Current supply chain structure based on the traditional batch production mode.

In order to provide a comprehensive characterization of the pharmaceutical industry supply chain and logistics, we first present a general view of the challenges and opportunities for improvement, along with a set of associated performance measures. From the analysed literature it seems there are two main levels of opportunities for improvement: the manufacturing level and the supply chain level.

At the manufacturing level, the main challenges include the minimization of production lead times and costs, more effective capacity utilization, the improvement of resource and energy efficiency, the improvement of production yields, the reduction of inventory levels and waste production, and an enhanced production flexibility and agility.

On the other hand, at the supply chain level, the most critical challenges include: the reduction of the supply chain complexity, the development of agile and more responsive supply chains, the minimization of production and distribution costs, the improvement of end-to-end visibility across the entire SC, fostering a seamless integration and coordination across the SC network, the inventory reduction in every node of the SC, and the integration of sustainability aspects.

Considering the three main pharmaceutical functional groups, analysed above, all challenges identified are summarized in Table 2.1.

Table 2.1 Challenges/opportunities for improvement, and current performance measures

Pharmaceutical function	Challenges	Acronym	Performance measures
R&D / Product Development	minimize time-to-market	TM	≈ 15 years[1]
	maximize the product pipeline value	PPV	- high phase III discontinuation - high commercial failures - drug benefits are not deemed to outweigh risks
	minimize development costs	DC	> $2,5 million per approved drug[2]
Manufacturing	minimize production lead times	LT	30 – 90 days[3]
	minimize production costs	PC	27-30% of sales[4]
	improve quality levels (excessive rework and discarded product)	Q	costs of rejected batches and rework estimated on 25% of revenue[5]
	minimize inventory levels	I	40-60 days[6]
	improve capacity utilization (OEE)	CU	OEE: 30%[7]
	improve resource and energy efficiency (improve production yields)	RU/Y	material efficiency: 1-10%[8]
	minimize waste production	WP	E-factor (API production): from 25 to higher than 100[9] (kg waste/kg product)
	improve production flexibility and agility	F	low responsiveness
Supply Chain	minimize the supply chain complexity	SCC	large manufacturing footprint / complex supply network
	minimize SC/distribution costs	DC	25% of pharma costs[10]
	development of agile and more responsive supply chains	R	1000-8000 h[11]

[1] Development cycle time considered since discovery to market launch Federsel, H.-J. (2009). "Chemical process research and development in the 21st century: challenges, strategies, and solutions from a pharmaceutical industry perspective." Acc. Chem. Res **42**(5): 671-680.
[2] DiMasi, J. A., H. G. Grabowski and R. W. Hansen (2016). "Innovation in the pharmaceutical industry: new estimates of R&D costs." Journal of health economics **47**: 20-33.
[3] Singh, M. P. (2005). The pharmaceutical supply chain: A diagnosis of the state-of-the-art, Massachusetts Institute of Technology.
[4] Basu, P., G. Joglekar, S. Rai, P. Suresh and J. Vernon (2008). "Analysis of manufacturing costs in pharmaceutical companies." Journal of Pharmaceutical Innovation **3**(1): 30-40.
[5] Harrington, T. S., L. Alinaghian and J. S. Srai (2014). Making the business case for continuous manufacturing in the Pharmaceutical Industry. Proceedings of the 25th Annual Production and Operations Management Society (POMS) Conference, Atlanta GA, May.
[6] Singh, M. P. (2005). The pharmaceutical supply chain: A diagnosis of the state-of-the-art, Massachusetts Institute of Technology.
[7] According to Vervaet, C. and J. P. Remon (2005). "Continuous granulation in the pharmaceutical industry." Chemical Engineering Science **60**(14): 3949-3957. 30% is the typical value in pharmaceutical industry, reaching a value of 74% in good manufacturing processes, and 92% in 'best-in-class' pharmaceutical production lines.
[8] Material efficiency considered as the amount of product produced per unit amount of materials used Shah, N. (2004). "Pharmaceutical supply chains: key issues and strategies for optimisation." Computers & chemical engineering **28**(6): 929-941.
[9] According to Dunn, P. J., A. Wells and M. T. Williams (2010). Green chemistry in the pharmaceutical industry, John Wiley & Sons., the E factor (kg waste/kg product) for the pharmaceutical industry range from 25 to higher than 100, being organic solvents the major contributor for the waste generated.
[10] Thomas, E., K. George, E. Larsen, K. Shah and D. Ungerman (2013). Building New Strengths in the Healthcare Supply Chain. Pharmaceuticals and Medical Products Operations. Mckinsey&Company, Mckinsey&Company.
[11] Supply chain cycle time considered as the elapsed time between material entering as raw material and leaving as product according to Shah, N. (2004). "Pharmaceutical supply chains: key issues and strategies for optimisation." Computers & chemical engineering **28**(6): 929-941.25

Pharmaceutical function	Challenges	Acronym	Performance measures
	improve end-to-end visibility across the entire SC	V	independent silos of activities
	seamless integration and coordination across the SC network	SI	independent silos of activities
	minimize inventory levels in every node of the supply chain	I	4-24 weeks' worth of finished good[12] 70 weeks E2E inventory[13]
	integration of sustainability aspects across the entire SC.	SSC	mainly economically issues (profit maximization or cost minimization)

2.2.3. Planning decision-making processes

2.2.3.1. Reference frameworks

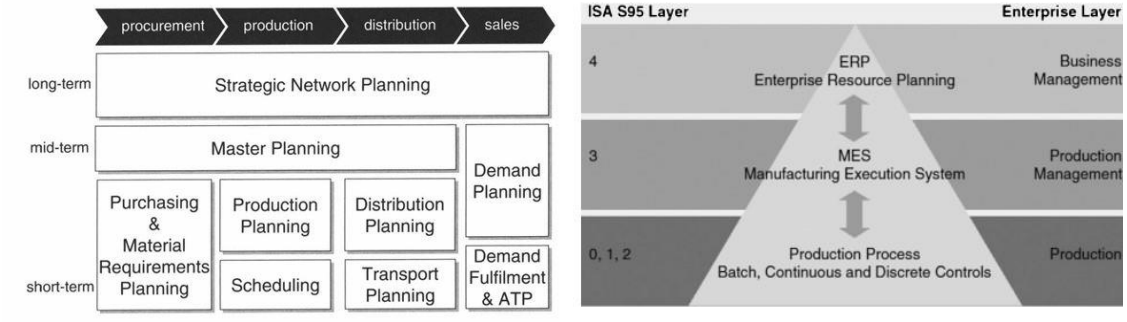
The decision-making processes (regardless of the industrial sector) span across different levels and problems to solve. These processes are highly dependent on how the problems themselves are constructed and on the specificities of the decisions involved. Problem construction, in one hand, will largely depend on a clear definition of the object of study, including the scope and the system boundaries, and on its formal conceptualization. Decisions may be more or less strategic, depending mainly on the impact that they will have on the company, on the time span needed for their implementation, and on the level of investment required. In this context, the way in which the supply chain runs and the way in which the analyst/modeller understands it are two inseparable attributes in the decision-making process. In short, to support an efficient planning of the supply chain operations, having a full understanding of the decision-making process is key.

Due to the complexity of supply chains, these decisions are usually grouped into different categories or taxonomies, embedded in matrices and frameworks that help researchers and practitioners to frame their decision problems. One of the widely accepted frameworks that have been developed is the well-known *supply chain planning matrix* proposed by Meyr et al. (2008) (see Figure 2.6(a)) that has been followed by researchers and practitioners to accommodate the majority of the decision problems arising in this context. This matrix summarizes three decision levels based on the length of the planning horizon, such as long-term decisions, medium-term decisions, and short-term decisions.

The long-term or strategic decisions encompass the design and structure of the supply chain, and typically involve large investments and long-term effects. The mid-term or tactical decisions are related to production planning with the main goal of meeting the targets established at the strategic level. The short-term or operational decisions specifically address individual activities/operations and their sequencing, in order to meet the production requirements defined at the tactical level.

[12] Ibid.
[13] Harrington, T. S., L. Alinaghian and J. S. Srai (2014). Making the business case for continuous manufacturing in the Pharmaceutical Industry. Proceedings of the 25th Annual Production and Operations Management Society (POMS) Conference, Atlanta GA, May.

Moreover, the hierarchical automation pyramid representation (ISA-S95 standard) is widely used as a reference to categorize the decisions involved in the supply chain management problems.



(a) (b)

Figure 2.6 (a) Supply chain planning framework (Meyr et al., 2008); and (b) Hierarchical automation pyramid (ISA-S95 standard) (Harjunkoski et al., 2014)

In a way similar to the Meyr et al. (2008) matrix, decisions are grouped into three enterprise levels, namely: the business management (long-term decisions), the production management (mid-term decisions) and production process (short-term decisions), see Figure 2.6(b). This hierarchical vertical perspective is the most widely used to accommodate the decision problems arising in the process industry, and has been the basis for many other adapted versions that have emerged over the years. Grossmann & Guillén-Gosálbez (2010) adapted this pyramid conceptualization to the hierarchical levels treated in PSE applications, considering single- and multi-site settings, and highlighted the role of an enterprise-wide optimization (EWO) perspective (Figure A.1 in Appendix A). Garcia & You (2015) presented a comprehensive overview of the main technical challenges and opportunities for supply chain design and optimization and presented a hierarchical pyramid similar to the previous authors (Grossmann & Guillén-Gosálbez, 2010) including at the top level the supply chain dimension (Figure A.2(a) in appendix A). The authors outline three major technical challenges in the supply chain design problem: multi-scale challenges, multi-objective and sustainability challenges, and multi-player challenges. However, these challenges are not explicitly reflected in the conceptualization depicted in Figure A.2(a). Moreover, Chu & You (2015) presented an interesting review of the progresses in integrated control and operations. The authors recognize the limitations of the ISA-S95 model (Figure 2.6 (b)) to characterize the decision levels, and categorized the current integrated methods based on modelling and optimization. In that sense, a more specific hierarchical structure was developed to accommodate the decision problems commonly investigated in integrated methods (Figure A.2(b) in Appendix A). Similarly to the model presented by Garcia & You (2015) at the top level, the authors included supply chain management.

All these models are based on a vertical hierarchical structure to accommodate the different decision levels. However, these levels are too broad to capture and categorize the current mix of complex decision problems and their integration, that currently dominate the pharmaceutical industry. Additionally, these representations tend to put the research focus into single and isolated problems

of the hierarchical model, that are solved sequentially in order to reduce complexity (Chu & You, 2015).

However, these approaches tend to lead to sub-optimal solutions or even infeasibilities because the interactions among all decision levels are neglected. In this regard Heintz et al. (2014) developed a more complete and interesting framework dedicated to the sustainable chemical product design activity, in order to enable the collaborative work across the chemical enterprise stakeholders at the different decision levels (Figure A.3 in Appendix A). The framework displays the vertical alignment of decisions with the enterprise layers and the three pillars of sustainability. In the following year, Moniz et al. (2015a) identified the critical factors that drive the planning and scheduling functions in the pharmaceutical industry and presented a conceptual representation (the *Delivery Trade-offs Matrix*) to support the management of the trade-offs occurring from the drug development process to commercial production (Figure A.4 in Appendix A).

A more recent perspective is presented by Harjunkoski (2017), assessing the impact of the recent "Internet of Things" developments on the traditional automation pyramid. According to (Harjunkoski, 2017) the different decision-levels will become more integrated and collaborative, blurring the traditional structural separation of the different hierarchical levels (Figure A.5 in Appendix A).

It is clear that these decision-level frameworks and conceptualizations are evolving over the years in an attempt to match the real challenges of the process industry, while giving shape and structure to the individual problems and their interactions. The current complexity in the pharmaceutical context, however, is still far from being captured by these models, that are too broad and disconnected from the functional enterprise organization and supply chain operational structure. The evolution in the company's organizational systems must be accompanied by the same level of development in the decision-making reference frameworks, and these should be able to efficiently accommodate the specificities of this sector.

2.2.3.2. Decision-making in the pharmaceutical industry

The The problems addressed in the pharmaceutical industry span across all decision-levels according to the more traditional vertical pyramid conceptualization described above, however with still very limited interaction between the levels and focusing on specific functional areas. In a recent work, Settanni et al. (2017) evaluate reconfiguration opportunities in pharmaceutical supply chains by critically mapping and categorizing the current pharmaceutical supply chain models. The authors acknowledge that the current definitions of the pharmaceutical supply chain are mainly based on a "*product-centric perspective and linear sequence of stages across the manufacture and physical distribution of medicines*". In addition, the analysis of the several reviews specifically dedicated to the pharmaceutical industry (Shah, 2004; Verderame et al., 2010; Laínez et al., 2012; Narayana et al., 2012; Narayana et al., 2014; Moniz et al., 2015c; Singh et al., 2016), reveals that research in this area has been covering several problems along the drug product life cycle (see Figure 2.3) without clearly

defining what has been, in fact, the main research focus of the academic community. A more comprehensive analysis of the literature is then required for a clear understanding of the planning problems structure in this sector.

Figure 2.7 depicts the distribution of the main published works across the pharmaceutical product life cycle. It contains full research works selected from the Scopus database, specifically addressing strategic, tactical and operational decision-making problems in the pharmaceutical industry. In order to provide a systematic characterization, works from the different perspectives (process system engineering, operations research, and supply chain management communities) are included. This search was done in May 2018 employing the following Boolean combination of keywords: *"planning" OR "scheduling" OR "decision-making" OR "supply chain") AND pharma.* The search was complemented by the analysis of several, selected review papers. A total of 113 papers were included in this analysis, after excluding duplicates, review papers, conference papers (some exceptions were admitted for works considered relevant for the analysis) and works exclusively related to management problems at the hospital/pharmacy level. The complete set of the selected publications is depicted in Table B.1 of Appendix B.

Analysing Figure 2.7 it is interesting to note that in the context of the pharmaceutical industry, the two extreme ends of the product life cycle have been the focus of the academic research, namely the R&D / New Product Development (NPD) phase, and the commercial production/distribution phase. Regarding the former, the most active sub-problems are the portfolio selection and scheduling of testing tasks, either individually or considered simultaneously. These problems have been mostly formulated as stochastic versions of the well-known Resource-Constrained Project Scheduling Problem (RCPSP), in which each product under development is considered a project with several tasks (product design and clinical trials) to be planned or scheduled. Recent works, however, include more sophisticated features such as task interdependency, outsourcing decisions, and risk management (Blau et al., 2004a; Colvin & Maravelias, 2011). Here, uncertainty has been modelled mainly by using stochastic programming, but other approaches can also be found, namely real option analysis (Rogers et al., 2002; Gupta & Maranas, 2004), robust optimization (Hassanzadeh et al., 2014), dynamic programming (Choi et al., 2004), or the emerging area of simulation-optimization based approaches (Blau et al., 2000; Subramanian et al., 2000; Subramanian et al., 2001; Subramanian et al., 2003; Blau et al., 2004a).

On the other hand, in Production/Distribution operations, the most addressed sub-problems are production planning and scheduling. In this case, the majority of the approaches employ MILP model formulations considering both, discrete- and continuous-time representations. The notably few works related to "global supply chain network design / capacity planning" are expected to consider the increasingly large-scale problems that typically arise from global pharmaceutical supply chains.

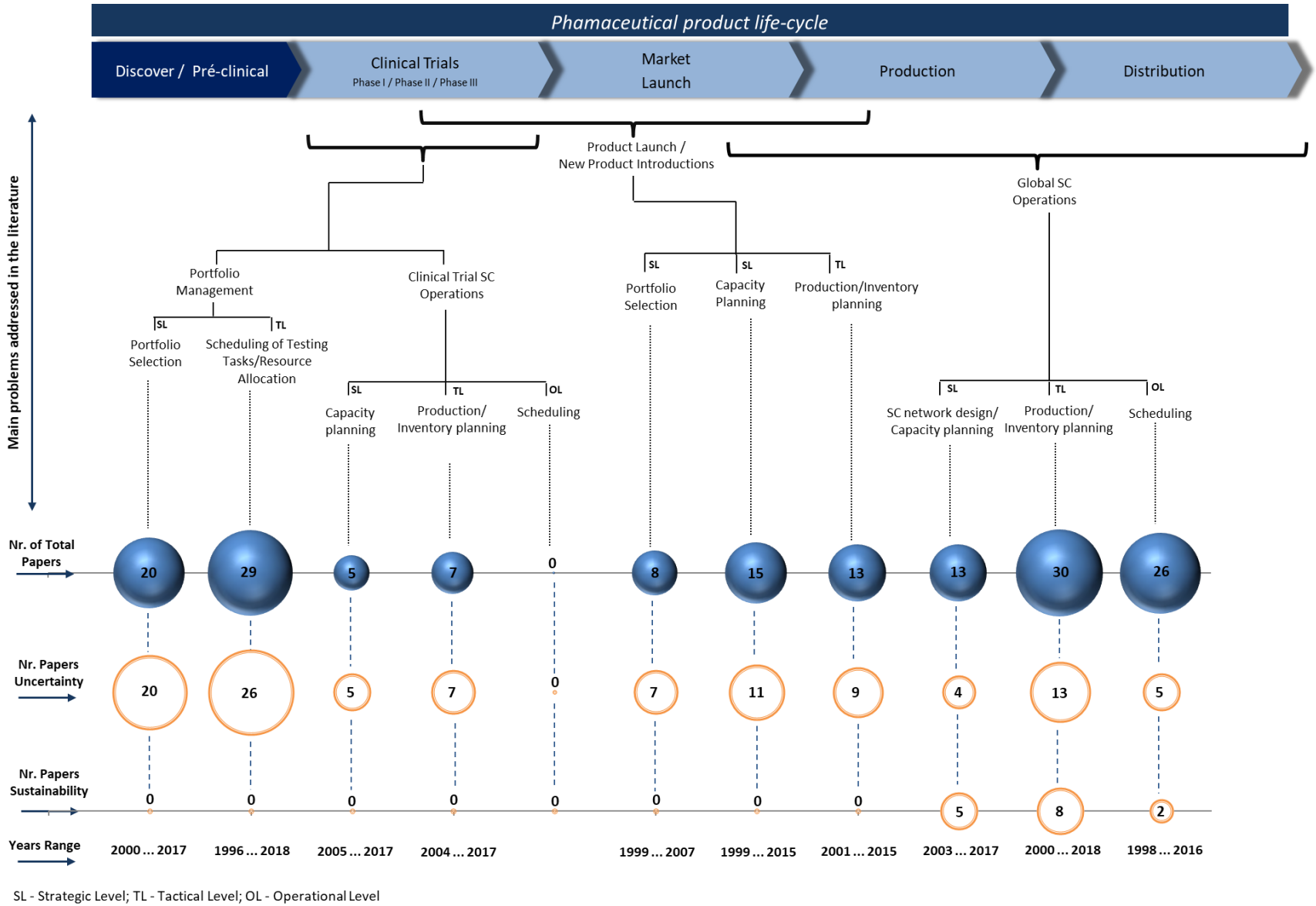


Figure 2.7 Main problems addressed in the literature.

Regarding uncertainty, a great discrepancy is observed between the NPD related work and the remaining studies (see Figure 2.7). This is mostly due to the high relevance of the technical uncertainty associated with the outcomes of the clinical trials during the development process. On the other hand, consideration of uncertainty in the commercial production/distribution level leads to greater complexity, particularly when dealing with multi-site, and/or multi-echelon settings. It is important to note that some major differences exist between innovators and generic manufacturers, regarding uncertainty. In the case of innovators, not only the obvious product development process is highly risky, but also the market in the commercial stage is highly uncertain. After product launch, the market needs first to grow, and then establish itself in a sustained way to face generic entrants in the near future. On the other hand, in the case of generic manufacturers, uncertainty plays a very different role in the sense that regulatory approval is much less risky and the market is already developed and well-established.

Nevertheless, the majority of the works dealing with uncertainty are still related to the innovators supply chain problems (Figure 2.7), with just a few exceptions explicitly dealing with planning problems associated to generic manufacturers (Stefansson et al., 2006; Stefansson et al., 2009; Jia & Zhao, 2017). Despite the major differences between these two supply chains, selected works show that the uncertainty issues related to generic supply chains are still very poorly explored or not explicitly addressed.

Concerning sustainability, from the total selected works there are only a few notable exceptions that explicitly integrate sustainability considerations into the developed framework, covering supply chains with reverse flows (Amaro & Barbosa-Póvoa, 2008; Amaro & Barbosa-Póvoa, 2009; Weraikat et al., 2016), efficient water and energy utilization (Halim & Srinivasan, 2011), waste management (Linninger et al., 2000; Linninger & Chakraborty, 2001), optimization of carbon emissions (Su et al., 2017; Zahiri et al., 2017), and socially responsible supply chains (Nematollahi et al., 2017; Nematollahi et al., 2018). All of these works, however, are only focused on the Production/Distribution operations. In the NPD phase, only modest considerations can be found in the form of penalty costs associated to waste generation due to the limited product lifetime or to the unused final product at the end of each trial (Fleischhacker & Zhao, 2011; Chen et al., 2012a; Chen et al., 2012b; Marques et al., 2017b).

Another interesting observation is that despite the increased interest in continuous manufacturing, very few works included in this analysis explicitly address planning problems in alternative technological settings or technology related decisions. Exceptions include the works of Sundaramoorthy et al. (2012) in which a capacity planning model for new product introductions is developed considering an integrated end-to-end continuous manufacturing scheme, Seifert et al. (2015) in which a real option framework for capacity expansion is developed and applied to the design of a continuous multiproduct plant, and Farid et al. (2005) in which a decision-support tool is developed for technology selection between a stainless steel pilot plant and disposable equipment for the production of clinical trial material.

This could be an indicator that research in continuous manufacturing is still very focused on "proof-of-concept" analysis, rather than in real practical applications (see Schaber et al. (2011), Srai et al. (2015b), Ierapetritou et al. (2016)), and reflecting also some caution in addressing this matter, due to the uncertainty that still exists associated to the supply chain implications of going continuous.

Additionally, this literature analysis also shows that the overall interest is mainly focused on efficiency improvement almost exclusively based on profit (NPV) maximization or cost minimization. Alternative performance metrics are seldom considered in the literature , as also noticed by Narayana et al. (2014).

Regarding multi-level, and cross-functional integration, only limited attention has been given over the years to these aspects. Despite the huge potential for value creation, also noticed by Varma et al. (2007) the published literature on integration of decision-making across the different decision-levels and enterprise functions is still very scarce.

The areas where decision-level integration is found are mainly in production planning and scheduling of the production/distribution functions (Berning et al., 2002; Stefansson et al., 2006; Amaro & Barbosa-Póvoa, 2008; Stefansson et al., 2009; Moniz et al., 2014a; Meiler et al., 2015; Vieira et al., 2016), and portfolio selection and scheduling of testing tasks/resource allocation in the product development functions (Blau et al., 2000; Subramanian et al., 2000; Blau et al., 2004a; Gupta & Maranas, 2004; George & Farid, 2008; Varma et al., 2008a; Perez-Escobedo et al., 2012; Zeng & Cremaschi, 2017).

Concerning cross-functional integration, the works explicitly addressing planning problems considering an enterprise-wide perspective are scarce and limited in scope. Even so, some noteworthy studies include the work of Maravelias & Grossmann (2001) in which an integrated approach is presented for the simultaneous planning of new product development and batch manufacturing facilities. The proposed model not only addresses the portfolio selection, resource allocation for the testing tasks, and the associated sequencing of the tests, but also the investment in new plants or the expansion of the existing ones to accommodate the commercial distribution of the new products, and the production plans for both, the new and existing products. Susarla & Karimi (2012a) developed an MILP model for enterprise-wide planning, considering the seamless coordination of several functional areas, such as procurement, production, distribution, and financial considerations (tax regulations). Moreover, Sousa et al. (2011) developed a model that optimizes the global supply chain planning of a pharmaceutical company, considering the coordination of primary and secondary production, distribution, and tax rates. Due to the large scale of the problem two decomposition approaches were proposed by the authors. Nevertheless, despite the relevant contributions of these works, none of them fully covers the complete enterprise-wide perspective, and only the work of Maravelias & Grossmann (2001) explicitly accounts for uncertainty.

Given this state of the literature, it is clear that many challenges still remain as open research opportunities needing to be addressed in this sector. In summary, these include: (i) greater attention

to integrated clinical trial supply chain operations management, and process development; (ii) improved approaches to assess and analyse the impacts of new product introductions in existing plants, covering global capacity and production planning decisions; (iii) development of effective approaches to tackle large-scale real industrial problems; (iv) development of systematic approaches for multi-level, multi-echelon, and cross-functional integration; (v) better exploitation and models of uncertainty in global supply chain operations; (vi) incorporation of sustainability issues such as environmental assessment and waste management, including over-supply related problems (such as the disposal of unused drugs and/or drugs past their expiry date), and social responsibility metrics across all functional areas and decision-levels; (vii) exploitation of different technological settings and incorporation of technological related decisions; (viii) introduction of alternative performance measures with relevance for the industry, including productivity, flexibility, and resiliency related metrics; (ix) development of powerful computational tools and solution methods to efficiently tackle all the above issues; and finally (x) the increasing availability of data with data acquisition and storage issues, and the development of new data-driven optimization approaches.

Tackling these research gaps, however, is becoming increasingly challenging as complexity grows fast, and the current decision-making reference frameworks have clear limitations to provide a systematic characterization of new problem structures.

2.3. Opportunities for change: driving forces and key enablers

For decades the pharmaceutical industry has benefited from a straightforward business model based on the discovery and development of high successful drugs (blockbuster drugs) with high profit margins. A good portion of these profits was then reinvested in R&D for financing the discovery of new drugs. Competition was almost entirely based on product innovation and new product introductions. At that point, production costs were considered as a small enough part of the companies' economic structure (compared for instance with the R&D costs), and operational or supply chain efficiency was not a priority for the decision-makers (Schaber et al., 2011; Berk et al., 2013). Consequently, the supply operations have been unchanged for decades, making both, the R&D and the manufacturing system, inefficient and unimproved for many years. However, the market conditions for pharmaceutical companies have significantly changed with the future trends suggesting fewer blockbusters, more specialty and personalized drug products, more stringent quality control, increased competition from generics, and more global and geographically dispersed markets (Srai et al., 2015a). The healthcare operating landscape is in clear transformation, and the new context has been shaped by many critical factors that were already pointed out by several authors (Shah, 2004; Laínez et al., 2012; Moniz et al., 2015c; Rogers & Ierapetritou, 2015; Srai et al., 2015a; Settanni et al., 2017). Not only have market and political factors provided driving forces for change, but also scientific and technological breakthroughs have served as enablers, defining new paths for the pharmaceutical industry and challenging its traditional business model. In the next sections these main drivers and enablers will be identified and described in detail.

2.3.1. Driving forces

Following the previous literature review, complemented by the analysis of several market reports (Berk et al., 2013; Jamie Cattell, 2013; Thomas et al., 2013; Alicke; et al., 2014; Little, 2016; Deloitte, 2016a; Deloitte, 2016b; EFPIA, 2017; Evaluate, 2017; Pharma, 2017; Deloitte, 2018; Dhankhar et al., 2018; Marwaha et al., 2018), nine driving forces were identified to have a significant impact on pharmaceutical supply chain operations. These forces will be classified according to two broad categories: *external drivers,* i.e., those which cannot be controlled by companies; and *internal drivers,* those that may be influenced to a certain extent by companies. As external drivers, the following were considered: (i) increasingly regulatory burden; (ii) pricing (and cost) pressures; (iii) growing personalized medicines; (iv) growth of emerging markets; (v) sustainability concerns; and (vi) increased uncertainty and risk. On the other hand, the following internal drivers were considered: (vii) declining R&D productivity; (viii) decreasing of effective patent life; and (ix) growing supply chain complexity. These driving forces will be presented in detail in the following sections.

2.3.1.1. External drivers

(i) Increasingly regulatory burden

The pharmaceutical industry is characterized by its robust and complex regulatory context, with patient safety as the central concern. Due to the potential of adverse effects on patient's health, new drugs are subject to very stringent regulations and clinical requirements, for both product and process development. Regulators, such as FDA and EMA, are putting a greater focus on pre-approval safety and efficacy evaluations, imposing more demanding protocols and quality criteria before market approval. Moreover, due to the higher complexity of the target diseases and new molecular entities, some extended trials to prove efficacy and long-term safety are now required, as well as post-approval mechanisms to monitor safety parameters (Kaitin, 2010; Khanna, 2012). Concerns are also present in logistics, with stricter regulations for storage areas with temperature and relative humidity monitoring. In addition, regional markets also have their own compulsory regulations and protocols to enable local commercialization, thus adding more complexity and further constraints to these already difficult processes.

Therefore, the entire regulatory framework has become very slow, expensive, and considered by the companies as one important factor for the lack of active innovation in the sector (Federsel, 2010).

However, despite these stringent regulations, regulators such as FDA or EMA are strongly committed in creating favourable conditions for innovation in both clinical trials and manufacturing processes. According to Lee et al. (2015) the vision for FDA's pharmaceutical quality for the 21st century is to promote a pharmaceutical sector with maximum efficiency, agility and flexibility, in producing high-quality drugs without extensive regulatory oversight. In this regard, the efforts of regulators to streamline the approval process by expedited review programs, have resulted for instance in the record number of 59 approved new drugs in 2018 (PMC, 2018; Mullard, 2019).

Even so, the current regulatory context and the corresponding demanding quality requirements are forcing companies to adapt and develop strategies to effectively meet these requirements, while improving productivity and operational efficiency.

(ii) Pricing (and resulting cost) pressures

The pharmaceutical industry has been under great pressure to reduce medicine prices, not only by the typical competition between pharmaceutical brands, but especially due to generics competition, government pressures and public health policies. Generic competition has become increasingly stronger, stimulated in part by legislation issued in 1984 that provided a pathway for competition once drug patents expired. as well as due to the increasing pressures for price reduction from national governments. (Grabowski & Vernon, 2000). Under present conditions, soon as the patent protection for a drug that has achieved a large enough market expires, generic manufacturers seek to enter the market. Without the associated costs of drug development, the generic companies are able to launch into the market bioequivalent drugs, with a lower price compared to the branded counterparts (Grabowski & Vernon, 2000).

The price of medicines has a significant impact on each country's economy. The high drug prices clearly increase the burden of government public expenditures in developed countries, and the affordability of medicines and its accessibility to the lower income populations play a critical role for the development of sustainable health care systems in emerging economies (Chen et al., 2018).

Accordingly, governments and citizens are constantly pressing pharmaceutical companies for price reduction and developing strategies, such as price cap regulations and reference prices to control and limit the pharmaceuticals expenditure (Chen et al., 2018). Each country's government defines and fixes the distribution margins at wholesalers, which can differ significantly from country to country depending on their domestic economy (EFPIA, 2017).

In that sense, pharmaceutical companies need, more than ever, to demonstrate real "value-for-money" through cost-effectiveness analysis when applying for market authorization in a specific country. The new drug must significantly improve current therapeutic practices or otherwise significantly reduce the therapeutic costs (Kaitin, 2010). In this way, many pricing strategies are already being "value-based" (or "outcome-based") with the price of medicines being directly linked not only to their economic value, but also to their demonstrated therapeutic value (Hulshof, 2014). This is not without controversy, as shown with several recent cases where the price of a new and highly effective drug was set on the basis of the savings in the costs achieved by less effective conventional therapies.

Especially in the case of generics, with much tighter profit margins, cost-effectiveness analysis is driving companies to develop strategies for cost reduction over the entire supply chain. Instead of the traditional product-centric perspective, companies are now starting to learn from other industrial sectors (both, in the chemical industrial sector and in other industries) that are highly focused on cost reduction and production efficiency.

In this regard the academic community and, in particular, the process systems engineering community has been playing a key role on the development of strategies and decision-making support tools focused on cost-reduction and overall operational efficiency. Works can be found specifically addressing a great variety of decision problems arising in the pharmaceutical industry, such as: (i) product portfolio and capacity management (Maravelias & Grossmann, 2001; Papageorgiou et al., 2001; Subramanian et al., 2001; Gatica et al., 2003b; Subramanian et al., 2003; Levis & Papageorgiou, 2004; Maravelias & Grossmann, 2004; Colvin & Maravelias, 2008; Colvin & Maravelias, 2009; Chen et al., 2012a; Perez-Escobedo et al., 2012); (ii) planning for new product introductions (Papageorgiou et al., 2001; Sundaramoorthy & Karimi, 2004; Hansen & Grunow, 2015b); (iii) Planning and scheduling (Lakhdar et al., 2006; Stefansson et al., 2006; Kopanos et al., 2010; Stefansson et al., 2011; Moniz et al., 2014a; Moniz et al., 2014c; Moniz et al., 2015c; Vieira et al., 2016); (iv) global supply chain network design and planning (Sousa et al., 2008; Sousa et al., 2011; Susarla & Karimi, 2012a); (v) supply chain with reverse flows (Amaro & Barbosa-Póvoa, 2008; Amaro & Barbosa-Póvoa, 2009); and (vi) incorporation of financial components in planning problems (Blau et al., 2004a; Guillén et al., 2006). Even though all the developments made so far, an effective modelling approaches to address real world large-scale problems still remain as an open challenge, together with cross-functional and decision-level integration (see section 2.2.3.2).

(iii) Growing Personalized medicines

Personalized medicine refers to medicines tailored to the genomic of each individual, contradicting the "one-size-fits-all" perspective and moving the traditional focus of reactive treatment of a disease to a proactive healthcare management concentrated on prevention and early treatment (Abrahams et al., 2005; Hamburg & Collins, 2010).

This type of approach has been a major trend in recent years, with the number of personalized medicines increasing steadily since 2008 (PMC, 2017). According to PMC (2018), the Personalized Medicine Coalition (PMC) classified 25 of the 59 new molecular entities approved by the FDA in 2018 (Mullard, 2019), as personalized medicines. This value accounts for about 42% of all new approvals in 2018, representing an increase from the 34% registered in 2017.

These trends are mainly due to the several benefits arising not only for patients with improved therapies, reduction of adverse reactions, and increased patient adherence to treatments, but also for the overall health care system with the potential overall cost reduction.

This paradigm change will obviously have a substantial impact on the current business model of innovators and on how the associated supply chains are designed and operated. Beyond the scientific and technological challenges, determining how to effectively and efficiently deliver this highly innovative medicines to patients in a large-scale perspective, i.e. how to move from mass production to mass customization, will be crucial to dictate which companies will succeed or fail in the future. Moreover, the traditional distribution network, with the wholesalers playing a central role, will inevitably suffer a shift to more direct distribution models (beginning and ending with the patient) as personalization increases.

At the quality level, an increase of quality data is expected, demanding for the development of better "track-and-trace" and on-line monitoring capabilities.

Despite the great challenges ahead, the benefits are very promising, particularly for the R&D and product development activities, in which a game-changing is expected to occur. Personalization will lower the risk and costs during clinical trials research, by steering research in the right direction with the selection of patients based on genetic characteristics instead of on the traditional "random" process (Abrahams et al., 2005; Davis et al., 2009). This can reduce the clinical trials size and complexity with a direct impact on the development costs and time-to-market, and at the same time, it can improve the probability of technical success and regulatory approval by avoiding patients susceptible to adverse reactions.

Nevertheless, despite the significant advancements in the development of personalized medicines and companion diagnostics, according to IQVIA (2019) the routine personalized treatment will not be expected within the next ten years. In fact, there are still some major challenges in terms of scientific and technological developments, regulatory policies, investment incentives, and reimbursement strategies.

(iv) Growth of emerging markets

The rapid economic growth of developing countries is also gradually improving their health care systems and shifting the growth opportunities for the medical drug market. In this environment, pharmaceutical companies are forced to rethink their manufacturing strategies and business models as their supply chains become even more global (Garnier, 2008; Ierapetritou et al., 2016). This expected increase on product demand will contribute to the retrofit of existing plants and optimized production processes, with increased process yields and assets utilization.

Emerging markets will also demand for new strategies to achieve affordable drug prices for the less-advantaged population, and to understand the specific needs of those patients, forcing companies to re-examine their supply models and distribution networks (Chen et al., 2018). This market expansion will also contribute to increase the risk of counterfeit drugs (Alicke; et al., 2014), demanding for greater transparency with an "end-to-end" supply chain monitoring and control.

In addition to these changes, academia will also need to adapt and shift from a research highly focused on operational efficiency improvement in developed economies, to embrace these new challenges imposed by the emerging markets.

(v) Sustainability concerns

Companies in all industrial sectors are increasingly aware of their economic, environmental and social responsibility, and their importance in achieving increased value and global success, far beyond the traditional financial dimension.

The process industry, and the pharmaceutical industry in particular, plays a significant role regarding sustainability issues, since it relies mainly on resource-intensive operations, typically with large

amounts of water, solvents and energy consumption. According to the 2030 agenda for sustainable development (UN, 2015), a substantial increase in resource-utilization efficiency should be achieved by 2030, as well as the implementation of actions to combat climate changes and their impacts. In that sense, companies are currently still facing great pressures to reduce their environmental impact, particularly regarding resources utilization and waste generation.

According to (Ott et al., 2014; Chaturvedi et al., 2017), the environmental impacts of the pharmaceutical industry are significant, with an *E* factor many times higher than that for oil refining and for bulk chemical industries. Furthermore, within pharmaceuticals also significant differences exist. Typically, biologics present *E* factors significantly higher than small molecule-based products, making the former environmentally more critical and, therefore, a priority from a sustainability perspective (Ramasamy et al., 2015; Budzinski et al., 2019).

The role of the Process System Engineering community has been crucial in this regard, by developing efficient decision-making tools and strategies covering different sustainability aspects and supply chain configurations (Bakshi & Fiksel, 2003). Its importance can be stressed by the amount of research work published over the years, and highlighted in several important reviews (Srivastava, 2007; Barbosa-Póvoa, 2009; Grossmann & Guillén-Gosálbez, 2010; Nikolopoulou & Ierapetritou, 2012b; Eskandarpour et al., 2015; Garcia & You, 2015; Barbosa-Póvoa et al., 2018).

Moreover, the increase of unused and expired drug products is pressing the pharmaceutical manufacturers to redesign their supply chains in order to adopt new eco-friendly technologies and to accommodate new activities, such as the collection, reintegration, and disposal of these products. Concepts such as "life cycle assessment" (Wernet et al., 2010; Ott et al., 2014), "reverse logistics" and "closed loop supply chains" (Amaro & Barbosa-Póvoa, 2008; Amaro & Barbosa-Póvoa, 2009; Kumar et al., 2009; Weraikat et al., 2016), particularly for the management of the growing problem of unused and/or expired drugs, are deserving a growing attention among the pharmaceutical community.

The rise of emerging economies will also generate new, important socio-economic challenges (Mani et al., 2018), putting the pharmaceutical industry in a privileged position to foster the adoption of business strategies that enable an efficient interaction between industry, society and ecosystems, leading to an end-to-end supply chain redesign.

(vi) Increased uncertainty and risk

Today's highly dynamic business context, with rapid political and socio-economic fast-changes, is raising uncertainty (or its perception) about the future among practitioners of all industrial sectors. Standing as an important concern for decision-makers, uncertainty is present in almost every practical problem across all decision-levels.

Particularly for the pharmaceutical industry, uncertainty is being increased by some break-out events with direct impact on the business context. The second patent cliff era between 2017 and 2022 as predicted in Pharma (2017), the rise of emerging markets, and the new digital based technologies are transforming this industry. Additionally, the prevalence of more complex molecular

entities and increased complexity of clinical trials, together with the rise of personalized therapies will contribute to increased uncertainty regarding the product portfolios of the future, and how the regulatory landscape will evolve to cope with product innovation. Moreover, not only the uncertainty associated with product development and the clinical trials outcomes, but also the uncertainty of market success after launch are factors making business decisions very challenging.

Several sources of uncertainty are arising, and a full understanding of these sources will be critical for effectively integrating uncertainty in decision-making processes. According to Garcia & You (2015), uncertainties can be viewed as strategic (associated to changes in the socio-political context, unpredictable events, climate effects, etc) and as operational (associated to changes in supply chain operations or execution strategies). In a similar way, Laínez et al. (2012) classifies uncertainties as external or internal. A different classification is presented by Jonsbråten (1998), based on the way uncertainty is resolved: exogenous uncertainty, in which realizations occur independently of process decisions; and endogenous uncertainty, in which realizations are dependent on process decisions.

Regardless of the classification used, efficient identification and management of all relevant sources of uncertainty is still a great challenge for practitioners and researchers. In particular, researchers have devoted increased attention to this issue over the years, with notable developments across the different decision-levels. Comprehensive reviews specifically devoted to optimization under uncertainty can be found in Powell (2018), Grossmann (2012), Grossmann et al. (2016b), Verderame et al. (2010), Li & Ierapetritou (2008) and Sahinidis (2004).

In a "big data" world, the ability to collect and access data efficiently will contribute to a better modeling of uncertainty, leveraging the development of new stochastic programming approaches. However, dealing with uncertainty is still an open research challenge, particularly in the context of real-world large-scale problems, clearly demanding for innovative approaches (Grossmann et al., 2016b; Powell, 2018).

2.3.1.2. Internal drivers

(vii) Declining of R&D productivity

In order to stay competitive and maintain revenue in stable levels, R&D should guarantee a continuous flow of new drugs to replace older drugs whose patents are expiring (Garnier, 2008; Paul et al., 2010a). According to Garnier (2008), the decline in R&D productivity is the central issue regarding pharmaceutical sustainability and competitiveness.

After a sharp decrease of 50% in drug approvals in the US in 2016 (from 56 in 2015 to 27 in 2016) (Pharma, 2017), a recover was observed in 2017, with 46 approved new drugs (Mullard, 2018) and a record number of 59 in 2018 (Mullard, 2019). However, according to (Mullard, 2019) the commercial potential of the 2018 approvals falls short of expectations, with the combined projected peak sales of the newly approved drugs being in decline.

The high investments in R&D, combined with the decrease in success rates during clinical development and the downfall in the recovery of investments, contribute to the low levels of productivity that have been experienced by the industry.

Together, the longer clinical trials, due to their increasingly complexity and dimension, the stringent regulatory requirements, the difficulty in addressing ever more challenging diseases, and the poor focus on target selection by the industry, have dramatically lowered the number of approved new drugs in recent years, standing at the basis of this productivity crisis (Garnier, 2008; Paul et al., 2010a; Bunnage, 2011; Pammolli et al., 2011b; DiMasi et al., 2016). Although scientific breakthroughs have raised the level of understanding of disease's mechanisms and improved the current analytical techniques, the significant variability across individuals and their behaviour towards diseases are still unsolved challenges that contribute to the persistent complexity of the drug innovation process (Gittelman, 2016).

The decline in R&D productivity has major consequences not only regarding the revenue and profit potential that is obviously compromised, but also regarding capacity management issues. Considering that the current installed infrastructure is sized for blockbuster volumes, the difference between new drug introductions and off patent drugs will result in an excess of production capacity of innovators. In that sense, efficient decision-making regarding the portfolio investment strategy is critical and should include market opportunity analysis, and regulatory and development aspects (Kaitin & DiMasi, 2011).

Companies should also become more focused, putting more effort towards larger unmet needs and smaller patients' populations, as it is the case of rare diseases. Recent estimates suggest that the orphan drug market (medicines aimed to target rare diseases) is expected to almost double during the 2016/2022 period (Evaluate, 2017). In addition, strategies such as the use of Contract Manufacturer Organizations (CMO) are raising among innovators, as they allow the introduction of new capacity as needed. In this way, the capacity management is shifted to the CMO, that is able to better balance capacity utilization by making products for multiple innovators. However, despite the importance of this issue for the pharmaceutical community, little attention has been given by researchers to the development of efficient decision-making tools for addressing product development and portfolio management, considering productivity as a central performance measure.

Some relevant works, can be found in the literature addressing different problems regarding new product development and pipeline management (Maravelias & Grossmann, 2001; Papageorgiou et al., 2001; Gatica et al., 2003b; Subramanian et al., 2003; Levis & Papageorgiou, 2004; Colvin & Maravelias, 2008; Chen et al., 2012a; Chen et al., 2012b), however, essentially focusing on total cost minimization or profit maximization.

(viii) Decreasing of effective patent life

Effective patent life can be measured as the time between regulatory approval and patent expiration (Grabowski & Vernon, 2000), and it represents the period of commercialization under patent

protection. The pharmaceutical industry is one of the most dependent on patent effective life, since it is during this period that the majority of the companies recover their investments. However, the long development cycles and the increasingly regulatory burden are delaying the time-to-market of new drugs, thus reducing the opportunity for companies to recover their investments under market exclusivity.

Time-to-market has been acknowledged by several authors (Shah, 2004; Moniz et al., 2015a) as the most critical issue in the pharmaceutical industry. Therefore, the current NPD model strictly focused on product innovation should also incorporate strategies to improve operational efficiency (such as the adoption of continuous manufacturing) in order to reduce not only the costs, but also the development cycle times. Currently, research addressing the product development process is mainly focused on cost reduction and portfolio management, with little attention being given to the reduction of the development cycle time.

(ix) Growing in SC complexity

The advent of globalization, the growth of emerging economies, and the increasing adoption of strategies such as mergers and acquisitions, outsourcing and licencing, have paved the way to larger, costly, and more complex global supply chains. It is common for big pharmaceuticals to have APIs being produced in several different countries that need to be transported to other facilities to formulate the final product, from there to packaging organizations, and finally to regional distribution centres and final customers.

The number of mergers and acquisitions (M&A) has increased substantially since the beginning of the twenty-first century and has been still rising in recent years (Blass, 2015; Wang et al., 2015). This strategy has been widely implemented by large pharmaceutical companies to face crises in R&D productivity. Particularly when approaching patent expirations of a major product, mergers become attractive in the sense that they can boost product portfolios, achieving capacity consolidation and exploiting economies of scale (Kaitin, 2010; Wang et al., 2015). Moreover, mergers and strategic alliances also contribute to develop new core competences, to expand the company's presence in emerging markets, as well as to gain market share in other sectors, such as generics and others (Tso & Jacob, 2012).

However, despite these potential benefits, M&A also contribute to a significant, uncontrolled increase in the organization's network, originating larger and more complex supply and distribution chains. This type of consolidation tends to result in redundant manufacturing facilities and capabilities, with lack of integration and a consolidate management (Tso & Jacob, 2012). Some studies suggest (Danzon et al., 2007; LaMattina, 2011; Sousa et al., 2011), that in the long-term mergers are unsuccessful in creating a positive pipeline value and in improving R&D productivity. Moreover, Sousa et al. (2011) advocates that the only way to improve profit margins, is by changing the relationship between volume and costs through productivity gains in the supply chain.

Other related strategies, such as outsourcing and alliances, as opposed to a fully integrated pharmaceutical company model, have been defended by some authors (Kaitin, 2010). According to Kaitin (2010), despite the increased complexity in supply chain management and coordination, these strategies can lead to a significant enhancement of production efficiency and speed to market.

In addition, more diverse markets, possibly resulting from the economic growth of emerging economies, will also increase complexity, leading to the emergence of new business models and strategies.

Due to this increasing complexity, not only the companies are struggling to efficiently manage all SC operations, but also researchers are being challenged to develop efficient decision-making tools covering the global SC management problems. In fact, the inherent large-scale of real problems tends to limit the number of published works addressing the entire pharmaceutical SC. Nevertheless, some interesting examples of these works can be found in (Timpe & Kallrath, 2000; Sundaramoorthy et al., 2006; Sousa et al., 2008; Sousa et al., 2011; Susarla & Karimi, 2012b).

2.3.2. Industry key enablers

Together with the above driving forces, technology breakthroughs are critical as key enablers of the inevitable changes towards a new paradigm.

If, on the one hand, these driving forces are pressing the industry to make a turnaround to stay competitive in the business environment in which it operates, on the other hand, technological developments are providing the necessary means to foster this change. Technology developments with direct impact on the pharmaceutical supply chain operations can be divided in three key areas: **product**, **process**, and **decision-making.**

The technology associated to the **product** is mainly related to the enhancement of new cell and genetic therapies that are enabling the personalization of medicines in an effort to match treatments to individual patients or small population niches with specific genome characteristics. Scientists are putting great focus on diagnostic tests based on genetics, to better predict patients' responses to target therapies (Hamburg & Collins, 2010). In this way, they are leveraging the medicines therapeutic value, as well as engaging more strategically with customers and fostering a patient-centric perspective. Personalized medicine is a current major trend and a rising market that will have also a significant impact at the supply operational level (see the "driving forces", section 2.3.1). Nevertheless, some challenges still need to be addressed at a scientific level, with greater understanding of the relation between genetic markers and clinical significance, and at an economical and operational level, as there is a poor alignment between the different stakeholders and the evidence of economic value (Davis et al., 2009). Moreover, at a regulatory level, there are interesting open issues on the definition and establishment of regulations and protocols capable of guaranteeing quality and patients safety, without compromising the necessary innovation character (Hamburg & Collins, 2010). Regulators such as FDA and EMA are strongly encouraging the development of personalized therapies, and they are truly engaged in creating the conditions and the

necessary regulatory landscape to help companies approach small niche therapeutic markets. For instance, the European agency EMA, through the program PRIME (PRIority MEdicines) launched in March 2016, aims at optimizing the development process and accelerate the market launch of innovative medicines that address unmet needs for very specific groups of patients, as it is the case of rare diseases (EMA, 2016).

At the **process-related technologies**, the most significant developments are in continuous manufacturing, and in the rising of digitalization with the Industry 4.0 revolution (including IoT, big data analytics, AI, cloud computing, and other related technologies).

The current state-of-the-art manufacturing technology for primary production in the pharmaceutical/biopharmaceutical industry is based on large scale batch stainless steel equipment. However, due to the already described low performance operational indicators, such as lack of agility, long lead times or high operational costs, together with the current market trends (see the "driving forces", section 2.3.1), the interest in implementing continuous manufacturing technologies has significantly raised in recent years.

Continuous manufacturing relies on the seamless flow of material between unit operations, undergoing different chemical/biological or physical processes, forming the final product in a continuous way. Thus, manufacturing is controlled by its production rate instead of its production volume (Nepveux et al., 2015). The most obvious effect is the elimination of the holding times between the "stop-and-start" steps involved in the batch production mode, with benefits not only on the production lead time and costs, but also on quality and safety aspects. A higher level of automation decreases the risk of human errors and enhances the quality and process control, with real-time monitoring of process parameters, and reduced variability between batches. Since, in this case, production does not depend on discrete sizes of processing units, higher flexibility is achieved for both, product and volume mix. This is particularly interesting to rapidly accommodate not only demand changes, but also innovative products such as personalized medicines or orphan drugs that will inevitably lead to high product variability, with very low volumes (niche markets).

Moreover, the intermediary stocks needed between each individual operation are eliminated in this case, thus reducing significantly the inventory level across the entire manufacturing process. The continuous flow of materials also enables higher throughputs, improved yields and purity, resulting in better resource and energy utilization. At the R&D level, continuous manufacturing will have a very significant impact by avoiding the need for complex, time consuming and costly *scale-ups* across the development cycle, as well as the *ramp-up* for commercialization. On the other hand, the manufacturing footprint is reduced, thus contributing to smaller and simpler supply chains.

These benefits have been widely recognized not only by the scientific community in some interesting recent works (Schaber et al., 2011; Klutz et al., 2015; Rogers & Ierapetritou, 2015; Adamo et al., 2016; Ierapetritou et al., 2016), but also by the regulatory entities that are strongly encouraging the adoption of continuous manufacturing, advocating for instance that it is strongly aligned with the

current Quality by Design (QbD) paradigm (Food & Administration, 2004; Lee et al., 2015) and that it can dramatically shorten the scale up time of newly approved drugs (National Academies of Sciences, 2019).

Together with continuous manufacturing technologies, single-use equipment has also attracted some attention by the scientific community, both separately or integrated with continuous manufacturing (Novais et al., 2001; Farid et al., 2005; Shukla & Gottschalk, 2013; Klutz et al., 2015).

Nevertheless, the lack of initiative by companies in adopting these technologies is well known, with adoption rates around 5%, basically related to pilot scale operations (Harrington et al., 2017). This low value has been mainly attributed to the regulatory burden, quality concerns, and to some major challenges, such as (Poechlauer et al., 2012; Lee et al., 2015; Nepveux et al., 2015): the higher level of process design (including on-line measurement systems) and process knowledge (including material characteristics, and knowledge of kinetic information regarding the unit operations) to guarantee the required product quality; the high initial investment needed; and the current available inventory of batch facilities that, according to Srai et al. (2015a) are currently sized for blockbuster supply in most of the big pharma companies.

Moreover, according to (National Academies of Sciences, 2019), the continuous manufacturing technology is gradually entering in the small molecule space, but still very far behind regarding biologics. The main reasons stand on the fact that, in the first case, the chemical reactions are well-defined and the critical quality attributes well-characterized. On the other hand, regarding biologics the biochemical processes involved are not so well-understood and the production processes are difficult to control.

Overall, continuous technologies for the secondary production have been much well accepted and developed, with significant progresses on the solid oral dosage forms of small molecules (Ierapetritou et al., 2016; Burcham et al., 2018; National Academies of Sciences, 2019). The few FDA approvals regarding continuous manufactured drugs are related to the secondary production of this type of products (Burcham et al., 2018).

In what concerns generic manufacturers, it is interesting to note that little attention has been given so far to the development of continuous manufacturing, even if its importance in delivering accessible drugs world-wide may be considered critical. The main features of this technology are summarized in Table C.1 - Appendix C.

Along with the industry trend of moving from batch operations to continuous operations, the *industry 4.0* revolution is also starting to emerge in the process industry. **Industry 4.0** envisions a decentralized self-organising and reconfigurable factory in which goods and machines are connected to each other in cyber-physical systems (CPS), communicating, exchanging data, triggering actions, and ultimately coordinating all manufacturing and supply chain operations by making decisions autonomously and intelligently (Kagermann et al., 2013). The benefits are huge and with great potential to help companies to cope with their current biggest challenges regarding operational

efficiency in an era of personalization and increased value. A comprehensive overview of the main benefits and challenges of this trend in the biopharmaceutical supply chains is made by Branke et al. (2016). Some of the main benefits include (see Table C.1 – Appendix C): real-time monitoring, enabling a better process control and adaptability to sources of variability; enhanced process safety and predictive maintenance, with self-aware production lines constantly monitoring themselves and reporting on their own condition; democratization of information and real-time flow of data (patient data, product data, process data, and supply chain operations data), a critical factor for the development of personalized therapies; enhanced track-and-trace capabilities; end-to-end supply chain visibility; and seamless coordination across all functional groups. All these benefits will contribute to a more flexible and responsive SC with greater operational efficiency, decentralized decision-making processes, new patient-oriented product-service solutions (linking diagnostics, devices, and drugs), and improved security and anti-counterfeiting systems (e.g. by the development of "smart" packaging).

According to some recent market studies (PwC, 2016; Deloitte, 2018; Marwaha et al., 2018) digitalization in the chemical and pharma industry is inevitable, and this will have an important role in the transition towards increased industrialisation (Branke et al., 2016).

However, the adoption of *industry 4.0* capabilities in process industries is not as straightforward as it is for instance in discrete industries (such as the automotive), and there is still a long way to go for the chemical and pharmaceutical sector. In order to fully embrace these new competencies and be part of the *industry 4.0* revolution, pharma companies need to undertake a complete change in their operating model and old manufacturing practices (such as batch processes) with an end-to-end redesign (Marwaha et al., 2018). Moreover, the lack of automation and virtual manufacturing technologies in this industry stand out as some of the most important adoption barriers (Marwaha et al., 2018). Thus, very few research projects have been published in the area so far, with the most relevant works starting to emerge in the chemical and petrochemical industry, particularly for fault detection/diagnosis applications (Li, 2016; Shu et al., 2016; Onel et al., 2018). Even so, some companies are already developing promising projects in this area. This is the case of BASF which, according to Deloitte (2016a), is already implementing these capabilities in a smart pilot plant in Kaiserslautern, through the mass customization of liquid soaps production without human involvement.

Finally, **decision-making capabilities** will form the link between all the above technologies in which modelling, optimization, and simulation together, with high performance computing, will stand as the basis for the decision-making processes. Even though IT tools, such as Enterprise Resource Planning (ERP) software, stand as paramount regarding an effective integration of information, they do not provide optimization capabilities for an effective decision-making (Grossmann, 2014; Moniz et al., 2014c).

Optimization based approaches in process system engineering rely largely on deterministic or stochastic Mixed Integer Linear and Non-linear Programming (MILP and MINLP) formulations and

decomposition techniques, such as Lagrangean or Benders decomposition, bi-level decomposition, and rolling horizon techniques (Grossmann, 2012). Several reviews on the developments in optimization models in the process industry have been published over the years. considering different modeling settings (Sahinidis, 2004; Méndez et al., 2006; Li & Ierapetritou, 2008; Verderame et al., 2010; Grossmann, 2012; Maravelias, 2012; Grossmann, 2014; Grossmann et al., 2016b).

Nevertheless, further improvements regarding optimization and mathematical programming applications still need to be made, in order to develop comprehensive decision-making support tools with real relevance for practitioners. Some current major challenges include (Grossmann, 2014; Garcia & You, 2015): (i) the effective integration and coordination across the company functional activities, and across several spatial (physical network of organizations) and temporal (SC decision-making levels) scales; (ii) appropriate modelling and integration of uncertainty; (iii) effective incorporation of sustainability and novel multi-objective approaches; (iv) new solution methods to solve large-scale complex problems; and finally (v) more powerful computational tools and decomposition techniques. With the increasing availability of data *(big data)*, novel modelling frameworks, computational algorithms, and data-driven optimization approaches are also emerging. Machine learning is one of the most growing technics, lying at the core of artificial intelligence and data science (Jordan & Mitchell, 2015), and has been also a major trend in process systems engineering (Lee et al., 2017). As a consequence, recent works have been published proposing decision-making frameworks that integrate machine learning and data science methods with optimization approaches, particularly to address uncertainty (Jiang & Guan, 2016; Ning & You, 2017; Ning & You, 2018).

Moreover, the *virtualization* of plants, supported by simulation, will play an important role not only to improve the overall SC operational performance, but also for training purposes, including the simulation of scale-up processes before their implementation, the exploitation of alternative reaction routes or operational processes, or even to assess process safety opportunities. Thus, on-line optimization and simulation-optimization models will be vital for the digitalization process. Many hybrid simulation-optimization approaches have been proposed in recent years, and several combinations between these two techniques are possible today as recently acknowledged by Figueira & Almada-Lobo (2014). Simulation-optimization based models in the chemical-pharmaceutical have been used to address different supply chain management problems (Jung et al., 2004; Nikolopoulou & Ierapetritou, 2012a; Chu et al., 2015b), clinical trials supply chain and capacity management (Chen et al., 2012a; Marques et al., 2017b; Marques et al., 2017a) or R&D pipeline management (Blau et al., 2000; Subramanian et al., 2001; Subramanian et al., 2003; Blau et al., 2004a).

To summarize, we may say that, as new paradigms emerge in the pharmaceutical business model and supply chain, new and more sophisticated modelling and optimization approaches are being developed to accurately capture all the materials and information flows across different time and geographical scales.

These three technological domains (product, process and decision-making) are evolving independently from each other, and may be considered, in some cases, as disruptive innovations. However, they need to be integrated in a fully collaborative way, in order to create real value in the pharmaceutical supply chain. Still, the development and application of innovative planning and scheduling tools to the current batch operations may introduce significant gains and achieve part of the benefits offered by continuous manufacturing.

2.3.3. Challenges, drivers and enablers impact Matrix

In order to systematize the great variety of issues to address, an *impact matrix* has been designed. In this matrix, both, drivers and enablers, are correlated with the industry *challenges* (Figure 2.8). The correlation is constructed considering 3 levels of impact on the industry challenges, namely *positive*, *negative*, and *not relevant*. The *positive* impact is considered when the driver/enabler has a positive effect towards the improvement of the challenge, and the *negative* impact is applied when it leads to a worse performance of the challenge.

An immediate observation is that the impacts of the *uncertainty*, and the *price/cost pressures* drivers are common to all functional areas, with the former contributing to a poor performance of the challenges, and the later with a generalized positive impact.

The *uncertainty* drivers may be viewed as disturbances to the system that cannot be controlled by the industry, but that must be anticipated and carefully managed. The current high level of uncertainty is a strong driver for a paradigm shift in the pharmaceutical industry, which has been poorly prepared to deal with risk (Dhankhar et al., 2018). In this way companies and researchers should invest in robust risk analysis and advanced risk management approaches to cope with the current uncertain environment. Regarding the *price/cost pressures,* these are market context drivers that are forcing companies to focus on efficiency across all functional areas.

From Figure 2.8 we can deduce that, for the R&D / Product Development functional group, the drivers *price/cost pressures*, *growing personalized medicines*, *declining R&D productivity*, and *decreasing of effective patent life*, put a mainly positive pressure in all the three challenge goals, while the drivers *increasing regulatory burden*, and *uncertainty* contribute to a poor performance of these challenges.

In what concerns the positive pressure drivers, the *market context* drivers are forcing the product development process to be both, cost-effective and product-effective, by developing target-specific medicines and covering unmet needs. In this way, the product development process is expected to evolve towards higher productivity levels, generating more value with less money. The last two drivers are internal, and they result from the poor performance that the current pharmaceutical industry faces. In that sense, they are industry self-motivated drivers in which improving the R&D / product development performance will inevitably lead to their decrease.

Symbol	
+	Positive Impact in challenges
–	Negative Impact in challenges
o	Not relevant Impact in challenges
♦	Strong relation
◊	Week relation
o	No relation

						R&D / Product Devlopment			Manufacturing								Supply Chain						
◊	♦	♦	o	(ix)	Growing in global SC complexity	o	o	o	o	o	o	o	o	o	o	o	–	–	–	–	–	–	–
♦	♦	♦	♦	(viii)	Decreasing of effective patent life	+	+	+	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
♦	♦	♦	♦	(vii)	Declining R&D productivity	+	+	+	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
♦	♦	♦	♦	(vi)	Uncertainty	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
♦	♦	♦	◊	(v)	Sustainability	o	o	o	o	+	o	+	+	+	+	o	+	+	+	o	o	+	+
♦	♦	♦	o	(iv)	Growing of emerging markets	o	o	o	+	+	–	–	o	o	o	+	–	–	+	–	–	–	+
◊	♦	♦	♦	(iii)	Growing personalized medicines	+	+	+	–	–	+	+	–	–	+	o	–	–	+	+	+	+	o
♦	♦	♦	◊	(ii)	Price/cost pressures	+	+	+	+	+	–	+	+	+	+	+	+	+	+	o	+	+	o
◊	♦	♦	♦	(i)	Increasing Regulatory Burden	–	–	–	–	–	+	o	o	o	o	–	–	–	–	o	o	o	o
						TM	DC	PPV	LT	PC	Q	I	CU	RU/Y	WP	F	SCC	DC	R	V	SI	I	SSC
						minimize time-to-market	minimize development costs	maximize the product pipeline value	minimize production lead times	minimize production costs	Improve quality levels	minimize inventory levels	improve capacity utilization (OEE)	improve resource and energy efficiency (improve production yields)	minimize waste production	improve production flexibility and agility	minimize the supply chain complexity	minimize distribution costs	development of agile and more responsive supply chains	improve end-to-end visibility across the entire SC	seamless integration and coordination across the SC network	mininimize inventory levels in every node of the supply chain	Integration of sustainability aspects across the entire SC.
						TM	DC	PPV	LT	PC	Q	I	CU	RU/Y	WP	F	SCC	DC	R	V	SI	I	SSC
					Cell and genetic therapy	+	+	+	o	o	+	+	o	o	+	o	o	o	o	o	o	+	o
					Continuous manufacturing	+	+	o	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
					Digitalization (Industry 4.0)	+	+	o	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
					Decision-making tools	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Decision-making tools
Digitalization (Industry 4.0)
Continuous manufacturing
Cell and genetic therapy

Drivers
Challenges
Enablers

Figure 2.8 Impact matrix – Drivers, Challenges and Enablers.

On the other hand, regarding the negative impact drivers, like *uncertainty* also the *increasing regulatory burden* driver can be seen as an external disturbance that must be carefully managed, in order to efficiently balance the compulsory requirements and their associated costs.

Concerning the *production* and *supply chain* functions, the drivers with the most significant impact on the industry challenges, in addition to the *uncertainty* and the *price/cost pressures* already mentioned, we have the *sustainability*, the *growing of personalized medicines* and the *growing of emerging markets*, with a mix of positive and negative impacts, depending on the challenge. The *sustainability* driver will have not only a direct positive impact on challenges such as the minimization of waste production, the improvement of resource and energy efficiency, and the integration of several sustainability aspects across the entire SC, but it may also contribute indirectly to the reduction of inventory levels in all SC nodes, and to the improvement of the capacity utilization of the processing units.

Growing of personalized medicines, on the other hand, is in some cases expected to impact more negatively, in the sense that it will disrupt the current production and supply chain paradigm, forcing a change from mass production to customized (low volume and high product mix) production. Regarding *growing of emerging markets*, the impact is also mostly negative due to the need to exploit new markets geographically dispersed. This will contribute to an increase of the SC complexity and of the distribution costs, and in the proliferation of counterfeit drugs. Nevertheless, a positive impact should be expected in the minimization of production costs due to pressures to increase affordability of new medicines in the emerging economies.

Finally, at the supply chain level, the *growing in SC complexity* driver will have a negative impact on all the identified challenges, as expected.

In what concerns the key technological enablers, all of them have a positive impact on the challenges, thus contributing to a generalized improvement of the performance indicators. The only exception is the *cell and genetic therapy* technology whose impact practically only affects the R&D / Product Development functional area.

This analysis allowed us to identify, in a systematic and structured way, the gaps that exist between the traditional operating modes still prevailing in the industry and the requirements and needs of the current market context. Filling these gaps is mandatory today, and accordingly companies should take advantage of the several technological breakthroughs as enablers to the construction of new operational strategies.

2.4. New paradigm in the Pharmaceutical Industry

The analysis of the impact matrix shows that the industry challenges, drivers, and enablers are forcing pharmaceutical companies to evolve from their traditional *product-centric* and *margin-driven* perspective to an *enterprise-wide* perspective in which cost reduction, resource efficiency, flexibility, speed to market, and sustainability issues are now considered as central concerns. Successful approaches that are already in place in the chemical industry, as well as in other manufacturing settings (e.g. discrete manufacturing), are now also being explored and implemented in the

pharmaceutical industry, as a way to benefit from strategies based on economies of scale and operational efficiency. Although this clear change in the direction of greater efficiency is already on the way, to precisely define what may be the future new operational paradigm seems to be a difficult or even impossible task. The expected operational changes can be challenging for a highly traditional industry, in which process innovation was almost inexistent for several years (Smith, 2005). As stated by Kaitin (2010) the big challenge for this industry will depend on its ability to develop new strategies and change an obsolete business model and an outdated R&D paradigm. Both functions, operations management and business strategy, will have to be perfectly aligned to be successful.

Nevertheless, we need to clearly identify the fundamental building components of the expected new paradigm, as well as its main impacts on the supply chain operations. Figure 2.9 depicts these components (6) viewed here as the main factors of this paradigm shift. Each of these factors has a very specific guiding focus, namely: outcome, efficiency, increased value, flexibility, market expansion, and overall welfare. Therefore, in line with these concerns, the new paradigm is expected to include the following models / strategic approaches (Figure 2.9): a patient-centric model, cost-driven operations, a targeted approach (as opposed to "blockbuster" drugs), outsourcing strategies, emphasis on emerging economies, and a sustainable mindset.

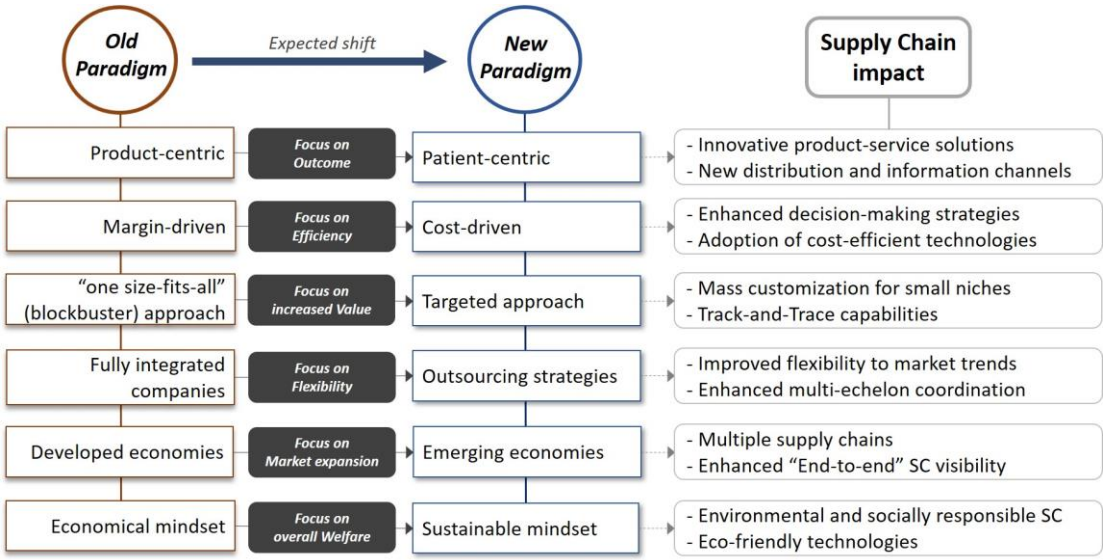


Figure 2.9 Paradigm shift and its impact on the pharmaceutical supply chain.

Regarding the patient-centric model, with the increased attention on outcomes instead of products, along with the emergence of "outcome-based" pricing models (see section 2.3.1.1) and Real-World-Evidence (RWE), the customer-experience is starting to arise as the centrepiece of the pharma business strategy. Accordingly, companies will need to engage more strategically with patients, fostering further understanding of their needs, expectations and fears in order to continuously revise and update their value propositions. New product-service solutions are expected by the exploitation of innovative technological breakthroughs (such as digital capabilities), and new distribution and

information channels will have to be created to increase patient's proximity and to build a trustful partnership with him. Extraordinary amounts of data will be available, and advanced analytics tools will be used to generate meaningful information and knowledge.

In what concerns the cost-driven approach, it is clear that operational efficiency is already catching the attention of pharmaceutical companies, that recognize the competitive advantage of capturing value from the supply chain. Advanced decision-making tools, together with innovative cost-efficient process technologies (such as continuous manufacturing), stand as key capabilities to achieve higher levels of cost-effectiveness. The ability to adopt innovative technologies and integrate those technologies with decision-making frameworks will surely dictate the company's operational success.

Moreover, the traditional primary care "blockbuster" model, which is highly risky today due to the lack of R&D productivity and its inability to replace the lost revenue from patent drops, is already changing. Companies are putting increased attention in value creation by a targeted approach essentially based on market segmentation and personalization. However, in order to effectively leverage product value, and even before the beginning of product development, companies should focus on two co-related endeavours. First they should identify the market specific unmet needs and the associated outcomes that are more valued by patients (both, in terms of therapeutic value and treatment comfort). Those needs should then be translated into product requirements to be incorporated in the final drug. Second, the company should focus on the patient's genome characteristics and, by exploring the universe of patients, identify those with greater potential for benefiting from the new drug.

In this way, the target-driven approach leverages the company's ability for differentiation from the competition by targeting both, the market unmet needs and personalized care.

Another shift from the "business as usual" that has also been observed in recent years is the rise of outsourcing and joint ventures strategies, moving from single to extended collaborative supply chains. Contract Manufacturing Organizations (CMOs) play a key role in this regard by providing faster and less expensive access to increased manufacturing capacity, and by making new technological capabilities available. In this way, pharmaceutical companies have more flexibility in reacting to market dynamics, and enhance their ability to manage risks more efficiently. Moreover, outsourcing strategies will also be crucial in providing local access to new markets. With emerging markets driving the most significant growth in the pharmaceutical industry, the business is clearly becoming more global and geographically spread. To cope with this increased complexity, companies will need to fully understand the cultures and the ways of doing business of the new markets, and will have to redesign their supply chains accordingly. Market segmentation and multiple distribution channels will be critical strategies for companies to secure drugs' access in remote places. And higher levels of transparency and "end-to-end" visibility will be required for an effective management and monitoring of the SC operations.

Finally, the last main component of the new pharma paradigm concerns the main responsibility of this industry in providing overall welfare, considering its environmental and social impacts.

Strategic decision-making should embrace environmental challenges and include eco-friendly strategies to reduce waste, minimize water and energy consumption, improve resource utilization, and achieve overall operational efficiency. Companies should also focus on innovative decision-making frameworks to responsibly address social issues such as affordability, availability, safety concerns, and generalized access to medicines (both physical and timely access).

All these strategic orientations, along with many other guidelines, are expected to arise in a shortcoming future as a result of the advent of the emerging *industry 4.0* (Branke et al., 2016), providing companies with new capabilities in core business dimensions.

The precise way in which all these contributions will be integrated and work together is obviously difficult to predict. However, it is clear that companies consistently adopting these principles will have an undeniable competitive advantage.

2.4.1. The future of supply chain operations

Based on this new paradigm, we made a thorough reflection on the impacts of these principles and tried to anticipate the structure and features of the future pharmaceutical supply chain.

According to Gautam & Pan (2016), the big pharma model is already changing to more lean and focused companies, with the specialty products and emerging markets growing as key revenue streams. The new pharmaceutical supply chain is then expected to be highly focused on patient and value deliver (Figure 2.9). Each individual patient will be expected to have an active role in every function of the company (marketing & sales, NPD, and operations) boosted by the growing adoption of a real-time flow of information on the patient needs and on the treatment outcomes. As depicted in Figure 2.10, the patient is understood here as the beginning and end of the entire supply chain, covering all enterprise-wide functions, as he is an active determinant in the identification of unmet needs, in the development of new drugs, and in the after launch long-term effect assessment.

The new supply chains should be designed based on market segmentation and on a "fit-for-purpose" strategy in which multiple distribution channels can be used according to each market segment. Both, primary care products for large populations and personalized care targeting small population niches, will exist in the global healthcare panorama, and companies need to be prepared, through resilient SC, to deal with these two scenarios simultaneously (see Figure 2.10).

Production will need to be more agile, flexible, and driven by efficiency and cost-reduction. A shift from exclusively based batch operations to continuous or semi-continuous operations is inevitable to improve efficiency and enable the accommodation of the required product/volume mix. Moreover, outsourcing strategies based on the establishment of trustful partnerships will be critical to achieve greater flexibility and attain the needed risk management competences.

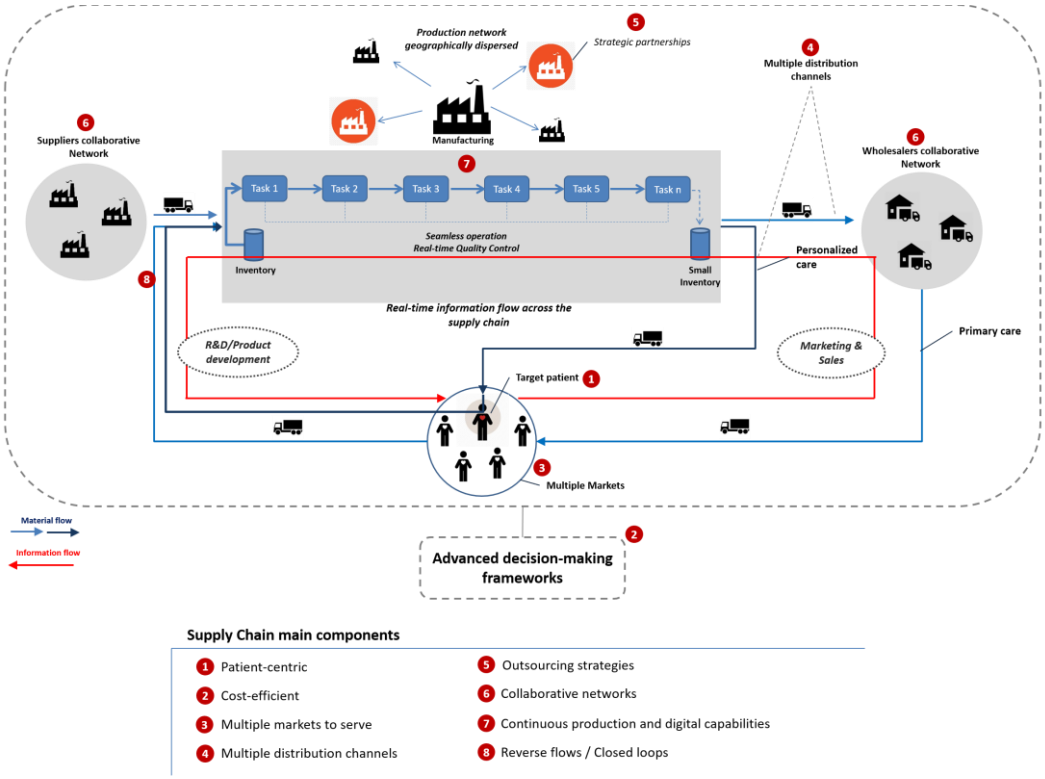


Figure 2.10 Schematic representation of the main components of the future pharmaceutical supply chain.

Improved "end-to-end" visibility and extended supply chain coordination will be paramount and achieved through the use of innovative technologies and digital capabilities responsible to generate, translate, and manage data from multiple sources (product, patient, enterprise).

Not only all the company functional activities, such as finance, marketing and sales, R&D and product development, and supply chain operations should communicate in an efficient and seamless way, but also the manufacturers, suppliers, wholesalers and other stakeholders should integrate collaborative networks as opposed to the strict supplier/customer relationship.

In this way, the new supply chains are expected to be more capable to deal with globalised, geographically dispersed manufacturing networks, hopefully depending on fewer and more efficient intermediates.

Finally, instead of the traditional linear sequence of stages, a circular approach is presented here, simultaneously fostering a sustainable perspective, with the reverse flows of materials, and a patient-centric perspective, with a real-time continuous flow of information (Figure 2.10).

All these characteristics are depicted in Figure 2.10, which is not intended to be a finished representation of the future pharmaceutical supply chain, but rather a schematic representation of the most relevant components to be considered, as opposed to the current supply chain depicted in Figure 2.5.

Together, the adoption of more cost-efficient technologies (such as continuous manufacturing), the incorporation of digital capabilities, and the exploitation of new distribution strategies less dependent on wholesalers (such as direct to patient distribution models), will be critical in reducing the manufacturing footprint, breaking out the silo-based perspective, and building up a sustainable operational mindset.

This future vision depicted in Figure 2.10 is already being pursued by several companies with several projects, showing this new path has very promising outcomes. In 2016, Johnson & Johnson received the first regulatory approval from FDA to switch from batch to continuous processing for the production of its HIV treatment Prevista (Hayek, 2017). Other companies are also investing in continuous manufacturing technologies at both laboratory and pilot-scale levels, such as Eli Lilly, GSK, Novartis, Pfizer, and others (Srai et al., 2015b).

2.4.2. Decision-making reference framework

The industrial standard hierarchical structure in which decisions span across three main levels (strategic, tactical, and operational) is no longer enough to deal with the multidimensionality of the problems faced today by the chemical-pharmaceutical industry. Strategic decisions (or long-term decisions) are not anymore exclusive of global supply chain management or of the plant design level, as presented in some existing conceptualizations (see Appendix I), but instead they cross all functional activities and echelons of the company (such as R&D, NPD, marketing, etc). Likewise, medium- and short-term decisions are also no longer exclusive of production planning and scheduling functions, but encompass a much wider scope. Moreover, the integration of the different decision levels is today an inevitable requirement to achieve a closer adherence to real-world problems. As also stated by Harjunkoski (2017), the structural separation of the hierarchical levels is becoming increasingly tenuous and questionable, as new digital technological breakthroughs emerge.

The current decision structure of a company is therefore much wider and complex, encompassing not only different time scales, but also different enterprise/business functions and activities, different scopes and impacts, different physical networks, and finally several technological settings.

The new reference model is, therefore, expected to be able to capture not only the main activities/processes, and entities/actors, but also their interdependencies and global context.

In that sense, we propose a novel conceptualization that seeks to deconstruct the hierarchical vertical perspective of decisions to give rise to a novel patient-centric layered approach, in which each layer corresponds to a specific dimension of the problem being addressed (Figure 2.11).

Grounded on the previous findings regarding the drivers and enablers impacting the industry challenges, and the lessons learned from the other industrial sectors, five building blocks were identified as being the foundations of the new reference model.

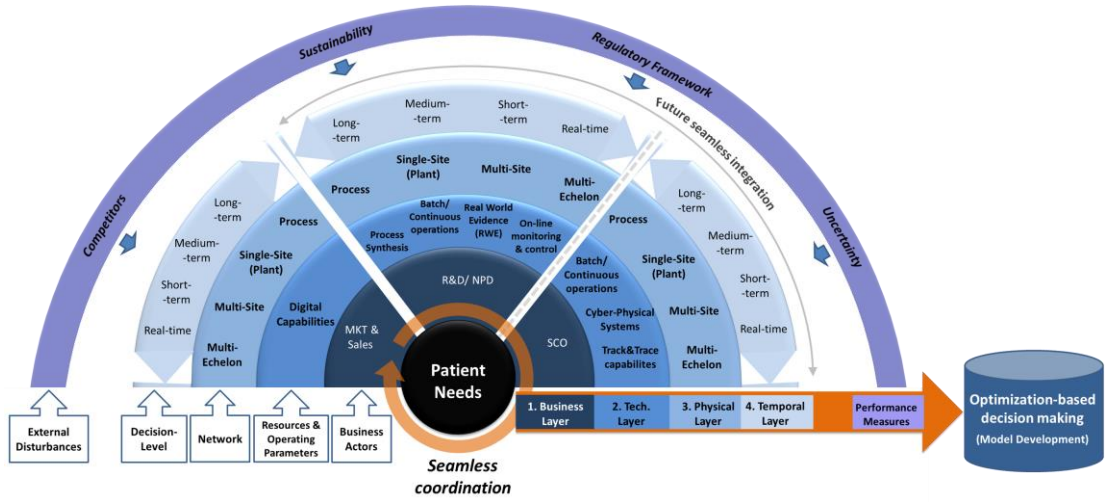


Figure 2.11 Decision-making reference model.

With the patient needs as the core of the decision-making process, each building block corresponds to a specific decision layer, through which problems will be defined, and optimization-based models developed. These building blocks are briefly described now:

0. Patient needs

In line with the expected new patient-centric business strategy, the proposed decision-making reference framework should be built around the patient needs and expectations. Being at the beginning and end of the supply chain network (

Figure 2.10), the patient will be the future main driver, not only in the definition of the product/service specifications, but also in setting some relevant operational performance metrics.

With an increasingly active role in the pharmaceutical SC, the patient is becoming more and more involved in the decision-making processes regarding his own health. Companies need, therefore, to incorporate his "voice" in the process, thus improving the customer experience, since the discovery process to the final delivery.

In this way, decision-making models will efficiently deal with issues such as higher product/volume mix, patient-centric distribution networks, more precise service levels, and real-time assessment of the overall customer-experience in closed-loops information channels.

1. Business layer

At the business layer, the description of the main functional areas of the company and the explicit representation of their interactions is highlighted. Within this layer we expect to position the problem being addressed within the main activities of the company, and explicitly consider the critical links between all the relevant activities and their interdependencies.

These activities are grouped here in three main functional areas as depicted in Figure 2.11, namely: Marketing, Sales and Finance; R&D and New Product Development; and Supply Chain Operations.

Each of these functional areas depends on its specific technological context and capabilities to achieve their goals, as explicitly addressed by the next layer.

2. Technological layer

The technological layer aims to describe all the company's established technological capabilities and to force researchers to incorporate those capabilities in their models in order to enhance the decision-making value.

The complete characterization of the technological capabilities inside the organization is vital to allow the different actors to jointly define the best optimization strategies. In this way, not only the batch/continuous operation modes need to be defined, but also the data acquisition systems and monitoring and control competencies should be rigorously characterized for a sound model development.

Moreover, considerations regarding the most relevant future capabilities (such as digital technologies) and technological-related decisions (such as technology selection) should be taken into account whenever possible, as a way to assess cost-effective and/or eco-friendly alternatives.

With the technological setting fully specified, the physical entities/facilities that host those technologies need to be carefully defined and characterized in terms of their spatial structure.

3. Physical layer

This layer describes the possible physical configurations of all supply chain entities and frames the decision problem in respect to the echelons considered in the analysis.

Decisions under the physical dimension may span from an individual "process" at the plant level to a geographically spread multi-echelon problem. The multiplicity of network configurations of *processes* within a manufacturing facility (single-site) and *facilities* in the same or different SC echelons (multi-site) is large and complex.

Whatever the network or sub-network configuration is, it needs to be optimized considering decisions that may span across all different temporal levels. For instance, at the strategic level, decisions can vary between network design in a multi-site configuration and technology selection if dealing with a single plant configuration. Likewise, at the operational level, decisions may span from routing plans (in a multi-site configuration) to production scheduling (at the plant level).

Significant modeling challenges may arise when dealing with large-scale networks in order to fully capture their complexities, particularly the interactions between the different SC echelons.

4. Temporal layer

The temporal layer describes decisions hierarchically, in terms of time, and for a given planning horizon. In this way, decisions can range from real-time (real-time monitoring and control) to several years (long-term strategic decisions). As depicted in Figure 2.11, this is the last layer in the problem definition and consequent model development. While the previous layers have as the most

prominent purpose the definition of the problem scope and its boundaries, in this case the most valuable outcome is a clear definition of the problem objective and its main constraints, considering all the previous assumptions.

Here, the external disturbances will have a significant impact that need to be explicitly accounted as described below.

5. External disturbances

Several external disturbances can affect the supply chain, with direct impact on its operational performance. In the proposed reference framework (Figure 2.11) four external factors are highlighted as the most relevant, namely: uncertainty (including external and internal uncertainty aspects); sustainability issues; regulatory framework; and market dynamics.

These factors have already been described in detail, and in particular they should be taken into account during system implementation. Nevertheless, despite their inherent complexity, they cannot be disregarded during model development, as they are always present and may significantly affect the system performance.

6. Seamless coordination

Finally, in the proposed reference framework (see Figure 2.11), "*seamless coordination*" is intended to reflect the major goal of achieving a fully integrated system, with global optimized operations across each dimension (layer) of the decision problem. In this way, optimization-based decision-making models should incorporate not only the more traditional cross-functional (business layer) and multi-level integration (temporal layer), but also a multi-echelon coordination (physical layer) and technology integration (technological layer). Additionally, with the rise of personalization, the patient will be closer to the production and distribution activities, leading to a growing approximation between product development operations and supply chain operations, hopefully towards a deeper, seamless integration.

Typically, integrated problems are currently solved by resorting to sequential methods, that seldom capture the links and interdependencies between the different levels, leading to sub-optimal or even inconsistent solutions (Chu & You, 2015). However, there are significant complexities even in each of these separate problem dimensions with its own scopes, scales and goals, and a single approach with such a high level of integration is yet to be developed.

At the business layer, data integration and real-time information sharing, across all company levels, is one of the main challenges when trying to achieve a higher level of collaboration (Dias & Ierapetritou, 2017). At the physical layer, the high dimensionality of the multi-echelon integration may be pointed as the main modelling challenge. Regarding multi-level (temporal) integration, it is clear that the different hierarchical decision-levels, although spanning across a wide time-scale, are highly interdependent. In this case, the major hurdle is possibly the way how the different temporal scales will be conjugated and modelled.

Full integration is still a great unsolved challenge, requiring the design of new sophisticated models and computational algorithms, and the implementation of enhanced decomposition techniques (Garcia & You, 2015; Dias & Ierapetritou, 2017).

2.4.3. Improvement assessment

Considering the expected evolution of the pharmaceutical supply chain and the proposed decision-making reference framework is possible to foresee the overall forthcoming gains at the several business levels (NPD, Manufacturing, and Supply Chain), as presented in Table 2.2.

The drug development process is expected to be more effective, with smaller and simpler trials, targeting specific patient characteristics and relying in evidence-based techniques (such as real-world evidence (RWE)) to support decision-making. Personalization will also reduce the risk of failure during trials, boosting faster product launches (thus reducing *time-to-market*) and contributing to decrease development costs.

The effective coordination between R&D and marketing in an effort to match drug development to market needs, will raise the likelihood of future commercial success and consequently increase the product pipeline value. Additionally, the adoption of continuous production modes will have a direct impact on the scale-up operations during development and on the *ramp-ups* after product launch, which will become considerably faster and simpler.

At the manufacturing level, we can anticipate a reduction of production costs, of production lead times, and of inventories, as a direct consequence of the adoption of more cost-efficient technologies (i.e. continuous manufacturing), and of the development of innovative decision-support tools, based on advanced optimization and simulation methods. Additionally, higher capacity utilizations are expected with improvements regarding energy and resource efficiency, as well as higher flexibility with improved responsiveness to market changes.

Finally, in what concerns the supply chain, the reduced footprint and complexity depicted in Figure 2.10 will definitely lead to a reduction in the distribution costs, inventory levels, and cycle times across the entire SC. Moreover, the new digital capabilities will contribute to enhanced end-to-end visibility and seamless coordination between all SC nodes and business functions. In this way, higher levels of operational efficiency will be achieved, and a greater quality control will be ensured.

Additionally, the adoption of market segmentation strategies and innovative distribution channels (e.g. directly to the patient) will contribute to avoid wholesalers' margins, reduce the overall distribution costs, improve patients' experience, and build patients' trust in the industry.

Table 2.2 shows the expected improvements in each of the industry challenges (as identified in section 2.2), based on several research works.

Table 2.2 Challenges/opportunities for improvement, current performance measures and expected improvements

Pharmaceutical function	Challenges	Acronym	Performance measures	Future expectation
R&D / Product Development	minimize time-to-market	TM	≈ 15 years[14]	<10 years[15]
	maximize the product pipeline value	PPV	- High phase III discontinuation - High commercial failures - Drug benefits are not deemed to outweigh risks	- Reduced clinical trial failures - Increased probability of market success - Increased patient
	minimize development costs	DC	> $2,5 million per approved drug[16]	≈ 10% reduction[17]
Manufacturing	minimize production lead times	LT	30 – 90 days[18]	60-80% reduction[19]
	minimize production costs	PC	27-30% of sales[20]	15-30% cost reduction[21]
	Improve quality levels (Excessive rework and discarded product)	Q	costs of rejected batches and rework estimated on 25% of revenue[22]	50% reduction in product deviations[23]
	minimize inventory levels	I	40-60 days[24]	Up to 50% reduction[25]
	improve capacity utilization (OEE)	CU	OEE: 30%[26]	move from 30% to more than 75%[27]
	improve resource and energy efficiency	RU/Y	material efficiency: 1-10%[28]	yield improvement of 10%[29]/

[14] Development cycle time considered since discovery to market launch Federsel, H.-J. (2009). "Chemical process research and development in the 21st century: challenges, strategies, and solutions from a pharmaceutical industry perspective." Acc. Chem. Res **42**(5): 671-680.
[15] Ibid.
[16] DiMasi, J. A., H. G. Grabowski and R. W. Hansen (2016). "Innovation in the pharmaceutical industry: new estimates of R&D costs." Journal of health economics **47**: 20-33.
[17] Harrington, T. S., L. Alinaghian and J. S. Srai (2014). Making the business case for continuous manufacturing in the Pharmaceutical Industry. Proceedings of the 25th Annual Production and Operations Management Society (POMS) Conference, Atlanta GA, May.
[18] Singh, M. P. (2005). The pharmaceutical supply chain: A diagnosis of the state-of-the-art, Massachusetts Institute of Technology.
[19] Hayek, M. (2017). "Continuous manufacturing: The clock is ticking. Is pharma ready?" ACCENTURE LIFE SCIENCES BLOG https://www.accenture.com/us-en/blogs/blogs-continuous-manufacturing-pharma-ready Accessed July, 2018 2018.
[20] Basu, P., G. Joglekar, S. Rai, P. Suresh and J. Vernon (2008). "Analysis of manufacturing costs in pharmaceutical companies." Journal of Pharmaceutical Innovation **3**(1): 30-40.
[21] Harrington, T. S., L. Alinaghian and J. S. Srai (2014). Making the business case for continuous manufacturing in the Pharmaceutical Industry. Proceedings of the 25th Annual Production and Operations Management Society (POMS) Conference, Atlanta GA, May, Hayek, M. (2017). "Continuous manufacturing: The clock is ticking. Is pharma ready?" ACCENTURE LIFE SCIENCES BLOG https://www.accenture.com/us-en/blogs/blogs-continuous-manufacturing-pharma-ready Accessed July, 2018 2018.
[22] Harrington, T. S., L. Alinaghian and J. S. Srai (2014). Making the business case for continuous manufacturing in the Pharmaceutical Industry. Proceedings of the 25th Annual Production and Operations Management Society (POMS) Conference, Atlanta GA, May.
[23] Hayek, M. (2017). "Continuous manufacturing: The clock is ticking. Is pharma ready?" ACCENTURE LIFE SCIENCES BLOG https://www.accenture.com/us-en/blogs/blogs-continuous-manufacturing-pharma-ready Accessed July, 2018 2018.
[24] Singh, M. P. (2005). The pharmaceutical supply chain: A diagnosis of the state-of-the-art, Massachusetts Institute of Technology.
[25] Srai, J. S., C. Badman, M. Krumme, M. Futran and C. Johnston (2015a). "Future Supply Chains Enabled by Continuous Processing—Opportunities Challenges May 20–21 2014 Continuous Manufacturing Symposium." Journal of Pharmaceutical Sciences **104**(3): 840-849.
[26] According to Vervaet, C. and J. P. Remon (2005). "Continuous granulation in the pharmaceutical industry." Chemical Engineering Science **60**(14): 3949-3957. 30% is the typical value in pharmaceutical industry, reaching a value of 74% in good manufacturing processes, and 92% in 'best-in-class' pharmaceutical production lines.
[27] Hayek, M. (2017). "Continuous manufacturing: The clock is ticking. Is pharma ready?" ACCENTURE LIFE SCIENCES BLOG https://www.accenture.com/us-en/blogs/blogs-continuous-manufacturing-pharma-ready Accessed July, 2018 2018.
[28] Material efficiency considered as the amount of product produced per unit amount of materials used Shah, N. (2004). "Pharmaceutical supply chains: key issues and strategies for optimisation." Computers & chemical engineering **28**(6): 929-941.
[29] Harrington, T. S., L. Alinaghian and J. S. Srai (2014). Making the business case for continuous manufacturing in the Pharmaceutical Industry. Proceedings of the 25th Annual Production and Operations Management Society (POMS) Conference, Atlanta GA, May.

Pharmaceutical function	Challenges	Acronym	Performance measures	Future expectation
	(improve production yields)			40% reduction in power consumption[30] and CO2 savings of 50%
	minimize waste production	WP	E-factor (API production): from 25 to higher than 100[31] (kg waste/kg product)	waste reductions highly dependent on the produced API[32]
	improve production flexibility and agility	F	low responsiveness	faster scale-ups and/or scale-downs in response to market disturbances
Supply Chain	minimize the supply chain complexity	SCC	large manufacturing footprint / Complex supply network	50-70% reduction in physical footprint[33]/ fewer SC actors more geographical dispersed
	minimize Supply Chain/Distribution costs	DC	25% of pharma costs[34]	15 – 20% [35] reduction
	development of agile and more responsive supply chains	R	1000-8000 h[36]	50-70% reduction in physical footprint[37]
	improve end-to-end visibility across the entire SC	V	independent silos of activities	seamless flow of information and cross-functional integration
	seamless integration and coordination across the SC network	SI	independent silos of activities	seamless flow of information and cross-functional integration
	minimize inventory levels in every node of the supply chain (E2E)	I	4-24 weeks' worth of finished good[38] 70 weeks E2E inventory[39]	up to 50% reduction[40]
	Integration of sustainability aspects across the entire SC.	SSC	mainly economically issues (profit maximization or cost minimization)	Integration of environmental and social indicators

[30] Hayek, M. (2017). "Continuous manufacturing: The clock is ticking. Is pharma ready?" ACCENTURE LIFE SCIENCES BLOG https://www.accenture.com/us-en/blogs/blogs-continuous-manufacturing-pharma-ready Accessed July, 2018 2018.
[31] According to Dunn, P. J., A. Wells and M. T. Williams (2010). Green chemistry in the pharmaceutical industry, John Wiley & Sons., the E factor (kg waste/kg product) for the pharmaceutical industry range from 25 to higher than 100 with organic solvents being the major contributor for the waste generated.
[32] Several studies have demonstrated the potential of continuous manufacturing in reducing the waste generated in API production. According to Gerogiorgis, D. I. and P. I. Barton (2009). Steady-state optimization of a continuous pharmaceutical process. Computer Aided Chemical Engineering, Elsevier. **27:** 927-932. one order of magnitude lower in waste generated was observed in the production of an innovative API when compared to the corresponding batch process. Also, Jolliffe, H. G. and D. I. Gerogiorgis (2016). "Process modelling and simulation for continuous pharmaceutical manufacturing of artemisinin." Chemical Engineering Research and Design **112**: 310-325. determined on average ≈ 66% less waste in the production of antimalarial substance artemisinin. In another study the same authors Jolliffe, H. G. and D. I. Gerogiorgis (2015). "Process modelling and simulation for continuous pharmaceutical manufacturing of ibuprofen." Chemical Engineering Research and Design **97**: 175-191. determined the E-factor value of 25.4 for the continuous production of ibuprofen, which is considerably low compared to many pharmaceutical processes.
[33] Hayek, M. (2017). "Continuous manufacturing: The clock is ticking. Is pharma ready?" ACCENTURE LIFE SCIENCES BLOG https://www.accenture.com/us-en/blogs/blogs-continuous-manufacturing-pharma-ready Accessed July, 2018 2018.
[34] Thomas, E., K. George, E. Larsen, K. Shah and D. Ungerman (2013). Building New Strengths in the Healthcare Supply Chain. Pharmaceuticals and Medical Products Operations. Mckinsey&Company, Mckinsey&Company.
[35] According to Deloitte (2016b). Innovative Routes to Market-Rethinking the Life Sciences Distribution Model. Innovative Routes to Market, Deloitte. a reduction in distribution costs of 15 - 20% is expected for the adoption of innovative routes to market, such as direct to patient distribution models.
[36] Supply chain cycle time considered as the elapsed time between material entering as raw material and leaving as product according to Shah, N. (2004). "Pharmaceutical supply chains: key issues and strategies for optimisation." Computers & chemical engineering **28**(6): 929-941.
[37] Hayek, M. (2017). "Continuous manufacturing: The clock is ticking. Is pharma ready?" ACCENTURE LIFE SCIENCES BLOG https://www.accenture.com/us-en/blogs/blogs-continuous-manufacturing-pharma-ready Accessed July, 2018 2018.
[38] Shah, N. (2004). "Pharmaceutical supply chains: key issues and strategies for optimisation." Computers & chemical engineering **28**(6): 929-941.
[39] Harrington, T. S., L. Alinaghian and J. S. Srai (2014). Making the business case for continuous manufacturing in the Pharmaceutical Industry. Proceedings of the 25th Annual Production and Operations Management Society (POMS) Conference, Atlanta GA, May.
[40] Srai, J. S., C. Badman, M. Krumme, M. Futran and C. Johnston (2015a). "Future Supply Chains Enabled by Continuous Processing—Opportunities Challenges May 20–21 2014 Continuous Manufacturing Symposium." Journal of Pharmaceutical Sciences **104**(3): 840-849.

2.5. Conclusion

This work presents a detailed analysis of the pharmaceutical industry's business environment, its supply chain operations, and related decision-making processes.

Within the industry's characterization, three main areas were identified as the most relevant, considering their impact on the industry's operational performance, namely: (i) product development and market launch; (ii) supply chain and logistics; and (iii) decision-making processes. In each of these areas, some research gaps and the key opportunities for improvement were identified, and then correlated with the most prevalent market drivers and technological enablers, in order to anticipate the industry's evolutive path to a new organizational paradigm. Following this, a new general decision-making reference framework, based on a patient-centric layered approach, is proposed, to give support to researchers and practitioners in structuring problems while considering all the current complexities of the industry,

The present study highlights the unprecedent changes currently faced by the pharmaceutical industry caused by today's business and market landscape. Conjunctural factors such as scientific and technological breakthroughs, increased societal pressures, stringent regulations, and a fast-changing market and competition environment, are considerably impacting the pharmaceutical supply chain operations and creating new, unexpected management challenges. In this context, the typical poor performance metrics of the industry are no longer acceptable, and new business strategies for its overall improvement seem inevitable.

It is clear that the industry is struggling to stay economically competitive, while maintaining the necessary levels of innovation needed to ensure R&D productivity.

Moreover, given the industry's fragilities and bottlenecks, the product development phase stands out as the most critical stage in the pharmaceutical product life-cycle, especially due to its essential role in providing new drugs to the market. Yet productivity metrics are seriously compromised with the increasing development costs and declining product pipeline value. At the manufacturing and supply chain level, significant opportunities for improvement were identified, and not taking advantage of those opportunities is greatly decreasing companies' ability to respond to market dynamics and securing their competitive positions.

Over the years, researchers and practitioners have been developing several positive approaches for the referred problems, thus contributing to higher levels of operational efficiency in the pharmaceutical industry. The amount of published papers addressing e.g. product portfolio management and production planning and scheduling during commercial manufacturing, shows already a certain level of maturity in the research interests around the pharmaceutical industry. However, our comprehensive literature survey also reveals that some pharmaceutical management issues are not yet duly covered, and that the current research is in general misaligned with the recent main trends driving the industry.

It seems, in fact, that little attention has been given to the patient-centric view and to new technological solutions, as part of alternative supply chains. Likewise, the increased importance of emerging markets does not seem to be accompanied by the academic community, typically focusing on the design of planning problems in developed economies. Moreover, the consideration of sustainability aspects beyond the purely economic dimension is still very poorly explored. This is particularly critical regarding social issues. As one of today's biggest challenges for the pharmaceutical companies is to broaden access and affordability of medicines by disadvantaged population, a social perspective is critical.

Moreover, the surveyed studies suggest a high influence of the traditional hierarchical vertical structure paradigm, with a little effort for the development of decision-making models and solution methods, in the case of the pharmaceutical industry. There is a clear lack of decision-level integration and functional coordination across the literature, and a deficit of attention to specific industry features such as lot traceability or process development considerations.

Therefore, and despite the difficulty in accurately predicting the future strategic path for the pharmaceutical industry, it is possible to foresee that a deep change in operations and decision-making processes will occur soon.

In this line, the decision-making reference framework proposed in this work aims at filling the existing gaps, by providing guidance for the "construction" of the relevant decision problems along their multiple dimensions. This new framework is able to capture all major aspects of the industry's behaviour and its supply chains, assisting managers and researchers in structuring problems and in focusing on the patient and his needs. In future research, we intend to incorporate some often neglected specific features of the pharmaceutical industry, such as its highly regulated nature, sustainability issues, complex uncertainty environments, resources and operational limitations, or technological settings.

In this way, the following chapters try to explore these new capabilities through the development of a decision-making tool applied to the NPD process, due to its importance in ensuring an efficient and timely product launch. Moreover, as depicted in Figure 2.7, planning for the clinical trials has been neglected over the years, thus evidencing a clear need for further development.

3. Stochastic product launch planning problem: A simulation-optimization approach

This chapter describes a new simulation-optimization based approach to tackle the pharmaceutical product launch planning problem under technical and market uncertainty.
The content of this chapter is based on the work published in an international peer reviewed journal and presented in two international conferences as follows:

Journal publication

Marques, C. M., Moniz, S., de Sousa, J. P., & Barbosa-Póvoa, A. P. (2017). A simulation optimization approach to integrate process design and planning decisions under technical and market uncertainties: A case from the chemical-pharmaceutical industry. Computers & Chemical Engineering, 106, 796-813.

Conference Proceedings

Marques, C. M., Moniz, S., de Sousa, J. P., & Barbosa-Póvoa, A. P. (2016). Optimization and Monte Carlo Simulation for Product Launch Planning under Uncertainty. In K. Zdravko & B. Miloš (Eds.), Computer Aided Chemical Engineering (Vol. Volume 38, pp. 421-426): Elsevier.

Marques, C. M., Moniz, S., de Sousa, J. P., & Barbosa-Póvoa, A. P. (2017). A simulation-optimization approach to integrate process design and planning decisions under technical and market uncertainties. In Foundations of Computer Aided Process Operations / Chemical Process Control. Tucson, Arizona.

Abstract

This chapter addresses the product-launch planning problem in the chemical-pharmaceutical industry under technical and market uncertainties and considering resource limitations associated to the need of processing in the same plant products under development and products in commercialization. A novel approach is developed by combining a mixed integer linear programming (MILP) model and a Monte Carlo simulation (MCS) procedure, to deal with the integrated process design and production planning decisions during the New Product Development (NPD) phase. The Monte Carlo simulation framework was designed as a two-step sampling procedure based on Bernoulli and Normal distributions. Results show the unquestionable influence of the uncertainty parameters on the decision variables and objective function, thus highlighting the inherent risks associated to the deterministic models. Process designs and scale-ups that maximize expected profit were determined, providing a valuable knowledge frame to support the long-term decision-making process, and enabling earlier and better decisions during NPD.

3.1. Introduction

3.1.1. Motivation

As acknowledge in the previous chapter, the pharmaceutical industry operates in a very dynamic, highly regulated and competitive business context, being one of the most important manufacturing sectors in Europe (EFPIA, 2016). The specificities of this industry are well known in the Process System Engineering (PSE) community. The heavy regulatory burden, high investment in R&D with very low success rates, and long periods for new product launch, clearly differentiate this industry from other sectors and impose significant managing challenges (Laínez et al., 2012). Furthermore, the liberalization of the global pharmaceutical market and the pressures of the regulatory agencies for a price reduction in medical drugs has paved the way to generic competition (Federsel, 2006). Considering the fact that the costs of imitation are extremely low when compared to the costs of innovation in pharmaceuticals, generic competition is becoming increasingly fierce, particularly regarding economic issues (Grabowski & Vernon, 2000). In that sense, this industry is now highly dependent on patent effective life, being forced to deliver medical drugs faster and more efficiently. As stated by Shah (2004) and more recently by (Moniz et al., 2015c), it is clear that *time-to-market* is the most critical issue in this industry, and that any delay associated with the product launch process entails a significant loss in future profits. This demanding business context has encouraged companies to invest in production capacity and to make process design decisions as early as possible, even before knowing if the products will ever reach the market (Kaminsky & Yuen, 2014). Those

decisions are thus highly risky, involving several sources of uncertainty that must be considered during the decision-making process (Moniz et al., 2015b).

In addition to the economic dimension of these decisions, sustainability concerns are also one main motivation of this work. In recent years a paradigm shift has been observed, with sustainability aspects being considered simultaneously with economic goals (Bakshi & Fiksel, 2003; Barbosa-Póvoa, 2012) Efficient resource utilization is becoming a global challenge, clearly reflected in the recent SPIRE (Sustainable Process Industry through Resource and Energy Efficiency) initiative, where the main goals towards improved efficiency and competitiveness are fully aligned with the European Horizon 2020 agenda (EC, 2013). The fine chemical and pharmaceutical industry plays an important role in this regard due to their high dependence on resources such as: water, raw materials and energy (Halim & Srinivasan, 2008; Wernet et al., 2010; Halim & Srinivasan, 2011). Thus, implementing efficient production planning decisions will definitely contribute to better resource utilization and waste minimization. More than ever, the need to achieve higher efficiency and cost savings in resource utilization, combined with the urgency in reducing the *time-to-market* of under development pharmaceutical products, clearly justifies further research in more advanced and reliable methods to solve real world planning optimization problems under uncertainty.

Accordingly, the work presented in this chapter addresses the product-launch planning problem, considering uncertainty on product demand and on the pass/fail outcomes of clinical trials. This work integrates process design and planning decisions, considering the resource limitations in processing, in the same plant, products under development and products already in commercialization. In practice, this approach provides contributions to enhance decision-making processes, with four overall goals: (i) maximize the profit of companies; (ii) minimize investments; (iii) minimize future changes in the production process; and (iv) to improve processes efficiency, particularly in what concerns resource utilization and waste reduction.

Therefore, improving the balance between available resources and product demand, while achieving interesting and sustainable results, is one of the main goals of the decision-making framework proposed here. The majority of currently available approaches are supported by deterministic models based on the maximization of expected values, without considering the highly stochastic nature of the problems (Li & Ierapetritou, 2008; Verderame et al., 2010). In this work, we have developed a MILP model for optimal product-launch planning, combined with a two-step MCS framework to tackle simultaneously different types of uncertainty.

3.1.2. Pharmaceutical Product Launch

3.1.2.1. New Product Development (NPD)

The development of new drugs is an expensive and time-consuming process that comprises several consecutive steps, already described in the previous chapter (see section 2.2.1), namely: discovery, pre-clinical tests, clinical trials, regulatory approval and market launch. Figure 3.1 depicts the pharmaceutical product lifecycle, since discovery to manufacturing and distribution, highlighting the

moments of scale-up decisions. According to Laínez et al. (2012), the time from discovery to market launch can take up to 15 years, and the average cost of a new drug is about US$ 2 billion and increasing, with about 50% representing clinical trial costs.

Clinical trials involve a series of very rigorous tests conducted on human beings, to assess the safety, efficacy and dosage levels of the new compound. These trials comprise three successive phases (I, II and III). In phase I, the new molecular entity is tested in 20/100 healthy volunteers, for safety assessment. In phase II, 100/500 volunteer patients are tested, to ensure the efficacy of the compound. Phase III usually involves thousands of volunteer patients, with the main purpose of comparing the performance of the new treatment with other existing treatments, and assessing its long-term effects (Levis & Papageorgiou, 2004; Colvin & Maravelias, 2008). The clinical trials process may take approximately 5 to 6 years (Colvin & Maravelias, 2008) and only after its successful completion and the FDA approval, the new compound is able to be commercially launched. In that sense, decisions such as "how much to produce?", "when to produce?" and "with what resources?" during the new product development process, are critical, and will have a significant impact on the company's sustainability. As failing a trial dosage can seriously compromise the *time-to-market* of the new drug, all the necessary resources need to be available as soon as they are needed (Levis & Papageorgiou, 2004). These decisions are, therefore, taken under significant levels of uncertainty, particularly regarding product demand. The high variability of product demand during clinical trials results mainly from the uncertainty of the pass/fail outcomes of clinical trials and is partially due to patient drop out during the progress of treatments (Chen et al., 2012a). On the other hand, if the compound fails at any clinical trial phase, the whole investment made until then is considered lost. This makes the NPD (New Product Development) stage one of the most critical in the whole product life cycle.

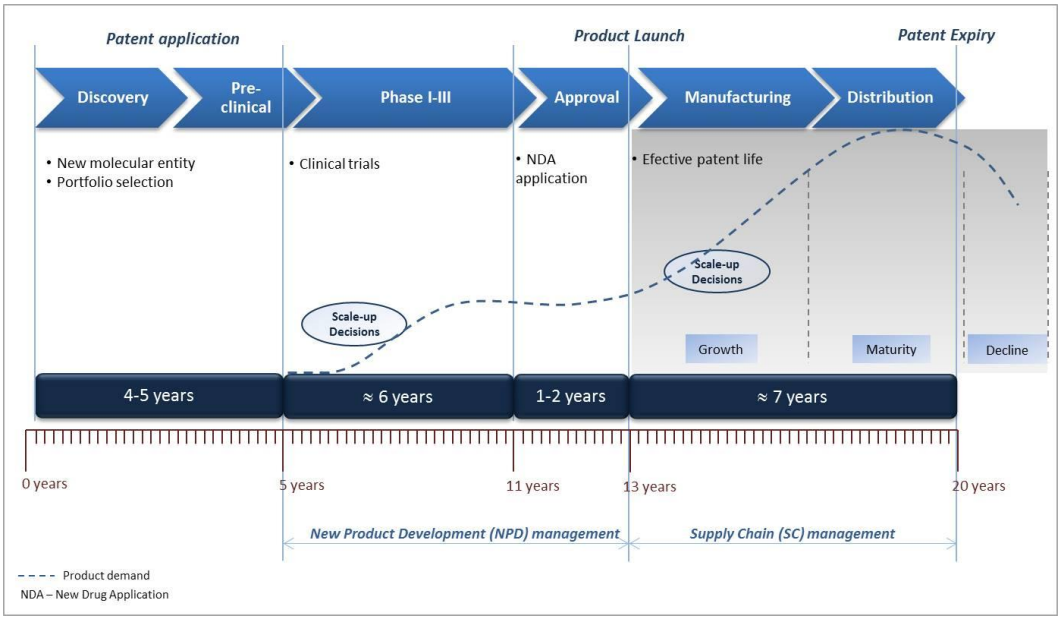


Figure 3.1 Pharmaceutical product lifecycle, highlighting the main scale-up decision moments.

3.1.2.2. Process Design

Along with the product development, also the production process for the new drug needs to be developed, in order to get the final approval by the regulatory agencies. Moreover, the company itself must also guarantee that it will be able to routinely manufacture reproducible batches of the new drug (Colvin & Maravelias, 2008). Traditionally, the pharmaceutical industry operates in batch and multipurpose production systems, simultaneously processing campaign and short-term modes (Moniz et al., 2014a) . In these plants, products already in commercialization and products under development compete for the same resources. In that sense, providing the right amount of resources, at the right moment, to each trial, represents a key management challenge, with the development of the production process playing a very critical role (Moniz et al., 2015b). The company starts by providing small amounts of the new product to the early stages of the clinical trials. Then it up-scales the process as needed to fulfill the last stages of product development and, finally, it has to guarantee the satisfaction of commercial demand, in terms of quantity and quality (Stonebraker, 2002). Process design and capacity decisions are therefore of paramount importance, and late-stage process changes will inevitably compromise the market launch of the new drug (Federsel, 2003).

Since changing the process after this being approved is very costly and complex, any poor decision taken during the early stages will have a huge impact in the commercialization phase. According to Federsel (2003), the process should be frozen no later than clinical trial phase II, in order to guarantee a drug production of good quality for long-term toxicology and stability testing. Therefore, in practice, these decisions are made with two conflicting objectives: (i) they should be sound and based on a considerable amount of information; and (ii) they should be made early enough to prevent any delays in the completion of the trials. According to Stonebraker (2002), the capital investments for the production facility usually occur around five years before the market launch of the new drug. As late decisions could significantly jeopardize the future incomes of the company, process design and capacity decisions, such as the assignment of processes to units, scale-up, and the acquisition of production units, have to be made under a significant uncertainty context.

3.2. Background

New product development management in the pharmaceutical industry has been one of the major concerns of the process system engineering community in recent years. In this area, the great majority of published works focus on product portfolio selection, on capacity planning, and on supply chain management during clinical trials (Laínez et al., 2012).

Typically, planning decisions are formulated as deterministic optimization problems in which all the parameters are assumed to be known. However, the importance of incorporating uncertainty into planning and scheduling models is increasingly recognized by the academic community (see some interesting, recent review articles such as Li & Ierapetritou (2008); Sahinidis (2004); Verderame et al. (2010)). Verderame et al. (2010) present a comprehensive overview of the main contributions in

planning and scheduling optimization under uncertainty, across multiple industrial sectors The most commonly used approach for planning under uncertainty is two-stage Stochastic Programming (SP) (Steimel & Engell, 2015). Planning decisions are typically taken in two stages, where strategic decisions ("here and now") are made in the first stage under significant uncertainty, and operational decisions ("wait and see") are made in a second stage after the resolution of the uncertainty. Usually, uncertainties are modelled as a set of discrete scenarios, as a way to account for all possible future outcomes, and each scenario is solved as a deterministic problem.

Rotstein et al. (1999) was one of the first papers addressing capacity planning under uncertainty in the outcomes of clinical trials. They developed a two-stage SP approach, with the first stage dealing with decisions such as product selection, initial capacity investment, and initial allocation of manufacturing resources to products. In a second stage, decisions are made after the completion of the clinical trials, and they include: additional capacity investments, re-allocation of manufacturing resources to products, and production plans. Papageorgiou et al. (2001) developed a MILP model to simultaneously address the selection of a product development and introduction strategy, and a long-term capacity planning and investment strategy, at multiple sites. However, this work does not account for the uncertainty associated to product demand or the outcomes of clinical trials. At the same time, Maravelias & Grossmann (2001) addressed the problem of simultaneously planning the new product development and the design of batch manufacturing facilities. The authors proposed a multi-period MILP model that maximizes the expected net present value of multiple projects (products under development). A two-stage stochastic optimization approach is adopted to account for the uncertainty in the outcome of the trials.

Gupta & Maranas (2000) also propose a two-stage SP approach, to address the multisite midterm supply-chain planning problem under demand uncertainty. The production decisions are made "here-and-now", and the supply chain (inventory and distribution) decisions are postponed as "wait-and-see". Later, the same authors (Rogers et al., 2002) presented a real-options strategy to determine the optimal product selection decisions in the pharmaceutical R&D portfolio management.

Gatica et al. (2003b) presented a multistage programming formulation for capacity planning with uncertainty associated to the outcomes of clinical trials. A scenario analysis was performed, and these uncertainty issues were modelled via a tree of scenarios. However, in this work only the outcomes of the last phase of clinical trials were considered, and this may obviously lead to suboptimal solutions. The same authors later presented (Gatica et al., 2003a) a scenario aggregation–disaggregation approach, with scenarios being grouped into predetermined clusters, based on a mapping procedure between products and the outcomes of clinical trials. Cheng et al. (2003) addressed the problem of designing and planning under market and technological uncertainty. The decision process explicitly incorporates both the upper-level investment decisions and the lower-level production decisions, as a two-stage optimization problem, with a multi-objective Markov chain. Later, Levis & Papageorgiou (2004) also proposed a two-stage, multi-scenario MILP model, to determine the product portfolio and to perform the multi-site capacity planning, considering uncertainty in the outcomes of clinical

trials. In the same year (Sundaramoorthy & Karimi, 2004) presented a multi-period, continuous-time MILP model to address the supply chain management problem in a pharmaceutical plant considering new product introductions (active ingredients or intermediates) and outsourcing. The model determines the production and inventory levels, and the level of outsourcing for existing intermediates to maximize gross profit. However, this work does not account for uncertainty, and it is assumed that the scale-up procedures are completed before the new product enters the facility for commercial production. A scenario-based multi-stage Stochastic Programming model was developed by Colvin & Maravelias (2008) for planning the clinical trials in the pharmaceutical R&D pipeline. The model determines which trials should be performed in each planning period, taking into account the uncertainty in the outcomes of the clinical trials. The authors use a reduced set of scenarios to limit the size of the problem. Later, they extend their work (Colvin & Maravelias, 2009) to simultaneously address the scheduling of clinical trials and resource planning. More recently, the same authors (Colvin & Maravelias, 2011) developed a multi-stage SP framework for R&D pipeline management, accounting for interdependencies between projects and tasks, and incorporating risk management considerations (both value-at-risk and conditional value-at-risk novel formulations). The main goal of this approach is to determine the schedule of tasks and make the resource planning decisions that maximize the Expected Net Present Value.

Lakhdar et al. (2006) presented another two-stage SP, by developing a MILP model based on Chance Constrained Programming (CCP), for medium-term planning of biopharmaceutical manufacturing with uncertainty on the fermentation titers. Later, Lakhdar & Papageorgiou (2008) presented a two-stage, multi-scenario MILP model for optimizing production plans in a biopharmaceutical manufacturing facility, addressing the same technical uncertainty. And more recently, Sundaramoorthy et al. (2012), developed a framework for capacity planning, ensuring the availability of enough resources for the foreseen product demand (a multi-scenario, multi-period MILP formulation, that takes into account uncertainty in the outcomes of clinical trials).

Although two stage stochastic programming approaches are still the most widely used, with some interesting results having been achieved in recent works, these procedures have important drawbacks that limit their full application. The need to generate a large number of scenarios significantly increases the model size, leading to formulations that are computationally intractable. Moreover, decisions such as how many scenarios to generate and which scenarios to generate are neither simple nor obvious, and the analysis of each scenario can be a very complex and time-consuming task. The inevitable increase in the number of scenarios, with the number of products and outcomes of the clinical trials, makes in fact this methodology less attractive to tackle many real problems.

Nevertheless, an interesting body of literature dedicated to *simulation-optimization* based approaches has emerged in the past years, to tackle some of the problems arising in new product development management. Subramanian et al. (2001) developed an approach (the “SIM-OPT” architecture) to address the R&D pipeline management problem. The approach combines

mathematical programming and discrete event system simulation, to tackle uncertainty and control the underlying risk. The concept of time lines is introduced to accommodate various stochastic realizations present in the R&D pipeline. Later, the same authors (Subramanian et al., 2003) extend their previous work to include methods for improvement of the stochastic optimization problem solution. (Jung et al., 2004) adopted part of the "SIM-OPT" architecture previously developed (Subramanian et al., 2001) to determine the safety stock levels under demand uncertainty in a chemical process industry supply chain. They have later extended their work to determine the safety stock levels in a multi-stage supply chain (Jung et al., 2008). Blau et al. (2004b) also addressed the product portfolio selection in the pharmaceutical industry, considering project uncertainties and dependencies. The developed approach combines a discrete event simulation with a genetic algorithm to select the optimal sequence of projects that maximizes the expected economic returns. (Choi et al., 2004) addressed the stochastic Resource-Constrained Project Scheduling Problem (RCPSP) using a discrete-time Markov chain for modeling uncertainties in task duration, cost and task results. A dynamic programing formulation, in a heuristically confined state space, was developed to solve the problem. (Rajapakse et al., 2005) developed a decision-making tool based on discrete event simulation to predict process and business outcomes of the biopharmaceutical drug development process. Wan et al. (2006a) developed a simulation based optimization approach to address multi-stage capacity expansion problems for risk management in the pharmaceutical product pipeline. (Varma et al., 2008a) also developed a computational framework (SIM-OPT), based on a combination of discrete event simulation and mixed integer programming, to address the joint optimization of scheduling and resource allocation decisions in the context of pharmaceutical R&D pipelines. More recently, Perez-Escobedo et al. (2012) developed a simulation-optimization approach combining a multi-objective Genetic Algorithm optimization framework coupled with a discrete event simulator to address the portfolio management and scheduling of new drugs in the pharmaceutical industry. In the same year, Chen et al. (2012a) addressed the clinical trial supply chain management problem, with a simulation-optimization framework that combines patient demand simulation, stochastic demand forecasting, a mathematical programming to optimize the production and distribution cost, and discrete event simulation to capture uncertainties.

Notwithstanding the important contributions of the above papers, most of the simulation-optimization approaches have been developed to address the R&D pipeline management and resource allocation (including portfolio selection and task scheduling decisions) and not the process design and production planning decisions at facility level (as addressed in this work). Moreover, the effect of resource sharing due to processing in the same plant products under development and products in commercialization, as well as the long-term capacity investment decisions (including scale-up analysis), are seldom considered in these works.

It seems clear that there is an evident scarcity of research in sound alternatives to the two-stage SP for simultaneously addressing process design and planning decisions, under market and technical uncertainties.

An alternative seems to be MCS (as proposed in this work), used to determine the impact of the uncertainty parameters, through the estimation of their probability distributions. Bassett et al. (1997) developed a framework for including uncertainty parameters into a general aggregate production planning procedure, or resource constrained scheduling problems, using MCS. The framework does not determine a specific schedule, but instead it determines robust operating policies that support the decision-making process. Farid et al. (2005) also used MCS to model technical and market uncertainties of biopharmaceutical batch manufacturing processes, based on a hierarchical framework. More recently, Eberle et al. (2014) proposed a framework for measuring and improving the production lead time of pharmaceutical processes, with MCS being applied to predict future total lead time based on probabilistic distributions. At the same time, Kaminsky & Yuen (2014) developed a model to address the problem of capacity investments during clinical trials, using a Bernoulli process with unknown rate. Through this model, the company re-evaluates its capacity investment strategy, as information about the potential success of the product is continually updated via the results of the clinical trials.

In the current work, an innovative approach to solve the product-launch planning problem in the pharmaceutical industry, under technical and market uncertainty is proposed. A mixed integer linear programming (MILP) model, incorporating Monte Carlo simulation (MCS), is developed for optimizing the process design decisions (process-unit allocation, scale-ups, and capacity planning) and for production planning. The proposed framework allows a deep investigation of a large number of possible values for the uncertainty parameters (instead of just scenarios) and provides a comprehensive analysis and assessment of the risks associated with these parameters.

3.3. Problem Statement

In order to increase economies, pharmaceutical production plants typically operate in batch and multi-purpose production systems, simultaneously processing, in the same plant, commercial and pilot scale (under development) products. In this production mode, a great variety of products can be produced by sharing all available resources (including processing units, raw materials, intermediaries, and utilities) with the same or different sequences of operations (Floudas & Lin (2004), Barbosa-Póvoa (2007)). Even if continuous manufacturing is currently a developing and promising area in the pharmaceutical industry, batch operating modes still prevail in this industrial sector (see Lee et al. (2015)).

We will therefore assume that, to adequately meet the demand requirements, plant resources are shared between these two types of products, with capacity expansions expected to accommodate this simultaneous production. Nevertheless, capacity expansions for the products in commercialization are, in general, highly undesirable. Not only because of the high costs involved in changing a production process that has already gained regulatory approval, but also because of the time consuming procedure of revalidating the process, whenever a modification is made. Therefore, the

model developed in this work will only allow capacity increases associated to the products under development.

The product development process considered here encompasses the three clinical trials phases and ends with the regulatory approval (of both product and production process) and the product launch.

In a typical pharmaceutical company, the development phase comprises a portfolio of products that are in different stages of development (different clinical trial phases), at any given time. Although the proposed model could be easily adapted for this situation, for the sake of clearness we will assume that a known set of products reaches phase I of the clinical trials at the same time, and that the optimal production plan is determined considering the probabilities of success of each product, at each phase of the clinical trials.

To accommodate all phases of the clinical trials, a planning horizon with several years is divided into equal time intervals ($t \in \mathbf{H}$). Due to the long time horizon imposed by clinical trials, demand uncertainty is considered for both types of products. For the products under development, uncertainty arises from two main sources: (i) outcomes of the clinical trials (pass/fail outcomes); and (ii) demand variability mainly due to patient drop out during the trials progress.

Moreover, *lot traceability* is also modelled in this work, due to its importance for the pharmaceutical industry. Nevertheless, a distinction should be made between *lots* and *task-batches*. According to Moniz et al. (2013a), the term "lot" refers to the total amount (quantity) of stable intermediary or final product that is produced following the known recipe (that includes the set of tasks, processing units, and materials). On the other hand, "task-batches" are limited by the capacity of the processing units and correspond to the amount of material produced by each task (tasks are elements of the production process of a lot). Thus, in order to ensure *lot traceability,* lots are associated to all materials, including raw materials, intermediaries and final products. In this work, lots are defined by the starting raw materials, with the availability of these materials being limited by predetermined lot-sizes. The model will select some of these lot-sizes in order to achieve the best trade-off between those sizes and the operational costs associated to the capacities of the processing units needed to process them.

In terms of storage policies, it is assumed that in each period, storage is only allowed for the final products in order to accommodate the demand variability. For the products under development, the excess of final product at the end of each clinical trial phase must be considered as wastage and discarded, since it cannot be reused. Thus, a critical balance between the amounts required for the trial and the additional costs associated with the leftovers at the end of each clinical trial, should be achieved by the model.

Regarding the production yields, a distinction between the two types of products is also made. For those under development, lower levels of production yields are considered due to their still premature manufacturing process when compared with the products already in commercialization.

The main goal of this planning process is to determine the "optimal" production plan, the process design, and production scale-ups for a set of products ($p \in P$), ensuring that all demand requirements are fulfilled. Because failures in the deliveries to the trials seriously compromise the time-to-market and the payback of the investments, we assume that all the demand requirements will be fulfilled for the under development products. Therefore, the problem addressed in this work is formally defined as follows.

Given:

(i) a fixed time horizon, discretized into several time periods of equal duration ($t \in \mathbf{H}$);
(ii) a set of under development products entering clinical trials ($p \in \mathbf{P}^{U}$);
(iii) a set of products already in commercialization ($p \in \mathbf{P}^{C}$);
(iv) the recipes of each final product ($p \in \mathbf{P}$);
(v) the lot sizes available for the raw materials of each product ($m \in \mathbf{W}_p$);
(vi) the set of processing units initially installed in the plant ($e \in \mathbf{E}$);
(vii) the maximum and minimum capacities of each processing unit;
(viii) the task suitability for every processing unit and the respective processing times;
(ix) the probabilistic distributions of the product demand;
(x) the probabilities of success of the under development products in each clinical trial phase;
(xi) all the operational and investment costs associated to each task and processing unit, as well as the sales prices of each product;

the key decisions for the product launch production planning problem are:

(i) best set of processing unit types for each process;
(ii) size and timings of scale-ups;
(iii) amount (quantity) to produce in each time period;
(iv) how much to store in each time period;
(v) capacity extension requirements for the under development products;

in order to maximize the Net Present Value (NPV) of the company operations related to these projects.

In light of the general decision-making reference framework proposed in the previous chapter, the problem being addressed can be positioned in the framework as depicted in Figure 3.2.

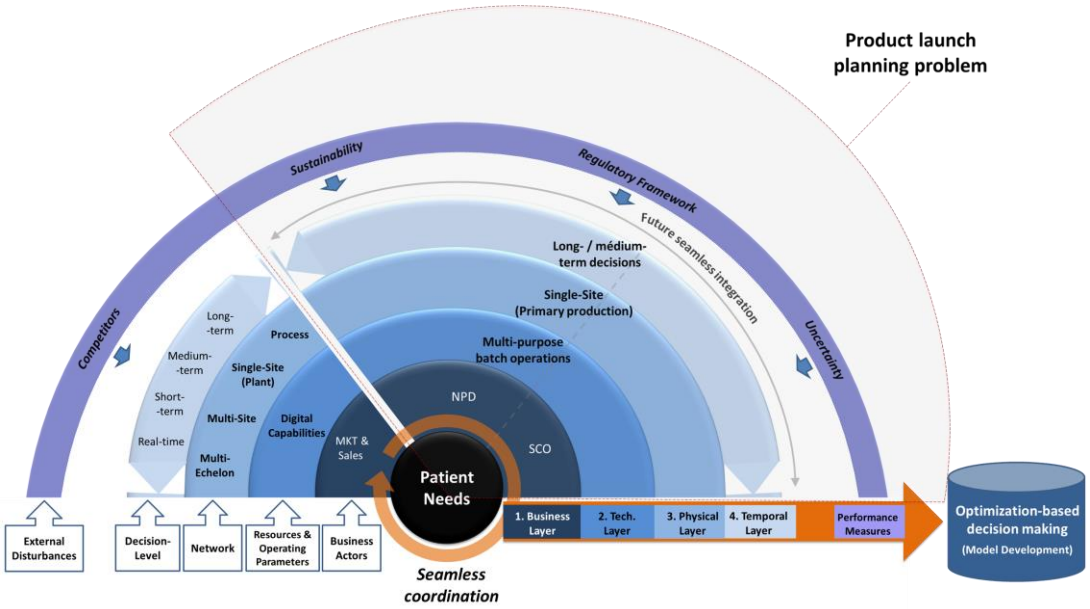


Figure 3.2 Problem positioning whithin the general refernce framework.

3.4. Proposed Method

3.4.1. A two-step MCS framework

The conceptual framework developed in this work integrates a MILP model with a two-step MCS. The MCS component randomly samples a large number of instances of product demand and outcomes of the clinical trials, until a stopping criterion is met. For each of these instances, the MILP model is solved and an optimal solution is obtained. The uncertainty parameters are randomly sampled from their given probabilistic distributions. Since normal distributions have been often used to capture the essential characteristics of product demand uncertainty (Wellons & Reklaitis (1989), Petkov & Maranas (1997), Gupta & Maranas (2003)), the *normality* assumption is also considered in this work. On the other hand, to model the uncertainty associated with the outcomes of the clinical trials, the probability of success of each product, at the end of the trial phases, is given by Bernoulli distributions, since there are only two possible results of the clinical tests: "success" or "failure".

For the products already in commercialization, only the demand is randomly sampled, but for those under development both uncertainty parameters (product demand and clinical trial outcomes) are randomly generated, in a two-step procedure performed for each clinical trial phase (see Figure 3.3). The random sampling for the product demand (step 1) is performed for each time period, while the sampling for the outcomes of the clinical trials (step 2) is performed only at the end of each clinical trial phase, as illustrated in the detailed diagram of Figure 3.4 (note that the procedure starts with the definition of the number of iterations to be performed).

In step 2, if the outcome of the clinical trial test is "pass", step 1 is performed again with the random generation of a value for the product demand for the next clinical trial phase, and so on. However, if the outcome is "fail", the two-step procedure stops (step 1 of the next trial phase will not be

performed) and the MILP model will be run considering that the demand for that product is zero for the following periods (this meaning that the development of this product will be abandoned). This procedure is executed for all products in each MCS iteration, and the MILP model is run considering the product demands obtained by this procedure.

At the end of the MCS procedure, we get the probability density function for the objective function, and the results for the probabilistic occurrence of the decision variables can be derived. These results are then analysed to support decision-making concerning the process design configuration, as well as the capacity and planning decisions during product development.

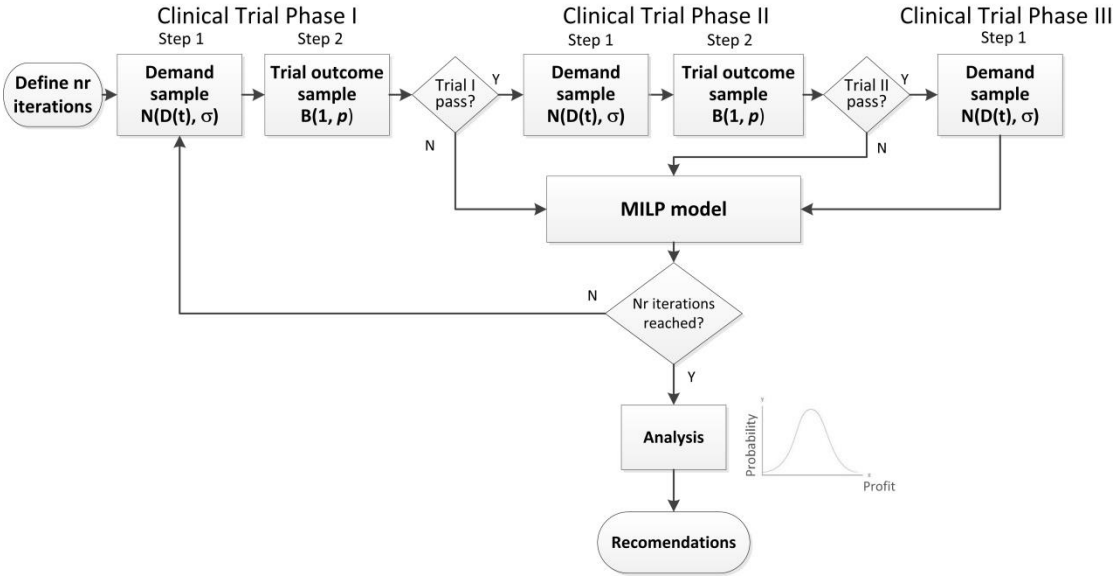


Figure 3.3 Schematic representation of the two-step MCS framework.

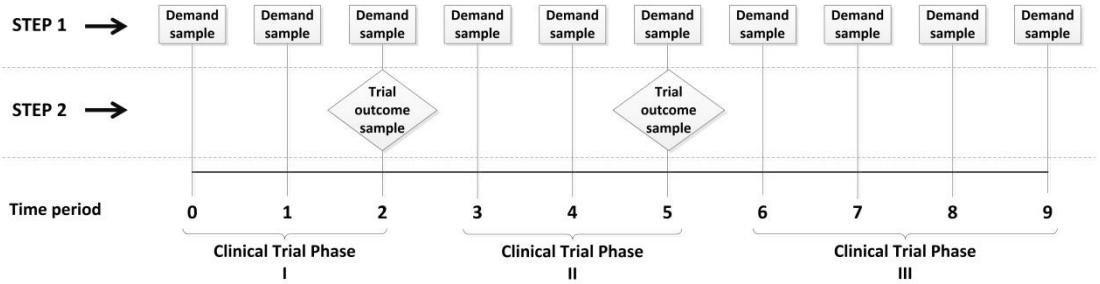


Figure 3.4 The two-step MCS procedure.

3.5. MILP Model

The optimal plan will be determined considering that resources are shared among the production of products under development and the production of products already in commercialization, over a planning horizon of several years. Thus, detailed time and task-sequencing constraints will not be

considered in this model. All material requirements, as well as all storage levels and production yields, will be precisely defined through the model parameters and decision variables.

The process design configuration and planning decisions are represented by the following decision variables:

- the *process/unit assignment* binary variables Y_{plet}, that are equal to 1 if product p of lot l is assigned to processing unit e in period t;
- the *task batch-size decisions* are associated to continuous variables B_{klt}, denoting the amount to be produced by each task k and lot l at period t;
- the *number of instances of each task k* of lot l are defined through the integer variables N_{klt} for each period t;
- the *lot-size decisions* are modelled by integer variables L_{mlt}, that define the number of lots of each lot-size l from a set of pre-determined lot sizes, for the starting raw material $m \in \mathbf{W}_p$ at each period t;
- the *excess resource* continuous variables R_{mlt}, that define the total amount available of material m of lot l at each period t;
- the *final product waste* continuous variables $W_{ml}|_{t=t_i^F}$, that denote the leftovers of the under development final products m ($m \in \mathbf{P^U}$) at the end of each clinical trial i (the final product that was not used during the clinical trial i and must be destroyed since it cannot be reused);
- *deliveries* are given by the continuous variables D_{mlt}, denoting the total amount of material m (final product) of lot l delivered at period t;
- the *unused capacity* continuous variables F_e, that define the amount of capacity not used by product p (products in commercialization) in processing unit e, and that will be available for the production of under development products;
- the *capacity extension* integer variables A_{et}, that define the number of additional processing units e to be added to the plant at period t.

The complete formulation encompasses constraints (3.1) to (3.15) and the objective function (3.16), as presented in the next section.

3.5.1. Mathematical formulation

NOTATION	
Indices	
e	Processing unit
i	Clinical trial phase
k	Processing task
l	Lot
m	Material (may be a raw material, an intermediary or a final product)

p	Final product
t	Period

Sets

$\mathbf{E}$	Processing units
$\mathbf{E}_p$	Processing units associated with product p
$\mathbf{E}_m$	Processing units associated with raw material $m \in \mathbf{W}$
$\mathbf{H}$	Planning horizon
$\mathbf{H}_i$	Time interval of the clinical trial phase i: $H_i = \{t_i^{initial}, \ldots, t_i^{Final}\}$
$\mathbf{I}$	Clinical trial phases
$\mathbf{K}$	Processing tasks
$\mathbf{K}_m$	Processing tasks associated with material m
$\mathbf{K}_e^{\boldsymbol{C}}$	Processing tasks of products in commercialization associated with processing unit e
$\mathbf{K}_e^{\boldsymbol{U}}$	Processing tasks of products under development associated with processing unit e
$\mathbf{L}$	Lots
$\mathbf{L}_m$	Lots associated with raw material $m \in \mathbf{W}$
$\mathbf{M}$	Materials including raw materials, intermediaries and final products
$\mathbf{P}$	Final products
$\mathbf{P}^{\mathbf{C}}$	Final products in commercialization
$\mathbf{P}^{\mathbf{U}}$	Final products under development
$\mathbf{W}$	Raw materials
$\mathbf{W}_p$	Raw materials of final product p

Parameters

v_{km}	Production rate (positive value for production, and negative value for consumption) of each task k and material m
τ	Length of each period
$\bar{\tau}_{ke}^{var}$	Time required per unit of processed material
τ^{chg}	Changeover time
$\hat{\tau}_e$	Installation and commissioning time of each processing unit e added to the plant
β_{ke}^{max} / β_{ke}^{min}	Maximum and minimum capacity for task k in processing unit e
μ_m^{max}	Maximum availability of material m
$\mu_m^{initial}$	Initial availability of material m
σ_{ml}	Lot size of lot l associated to raw material $m \in \mathbf{W}$
ω_{mt}	Product demand for material m at period t
θ_i^I /θ_i^F	Initial and final times for clinical trial phase i
γ_{mt}	Maximum number of lots for raw material $m \in \mathbf{W}$ at period t
δ_e^{init}	Number of processing units e initially available
π_m	Sales price for materials $m \in \mathbf{P}$
$\alpha_k^{oper.}$	Operational cost of each processing task k
$\alpha_m^{stor.}$	Storage cost for each material m
α_m^{waste}	Cost of disposing each unit of material m
α_e^{chg}	Changeover costs associated to each processing unit e
$\alpha_{ml}^{lot\ size}$	Cost associated with the lot size l for raw material $m \in \mathbf{W}$
$\alpha_e^{invest.}$	Investment costs for each new additional processing unit e

Continuous variables

B_{klt}	Batch size of task *k* of lot *l* at period *t,* expressed in kg
D_{mlt}	Amount delivered of each material *m* of lot *l* at period *t*, expressed in kg
R_{mlt}	Excess resource for each material *m* of lot *l* at each period *t*, expressed in kg
$W_{ml}\|_{t=t_i^F}$	Excess amount of final product under development ($m \in \mathbf{P^U}$) of lot l considered waste at the end of each clinical trial *i* ($t = t_i^F$), expressed in kg
F_e	Capacity unused for each processing unit *e*, expressed in hours

Binary variables

Y_{plet}	=1 if product *p* is assigned to processing unit *e* and lot *l,* at period *t*

Integer variables

N_{klt}	Number of instances of task *k* of lot *l* at period *t*
A_{et}	Number of additional processing units *e* to add to the plant at period *t*
L_{mlt}	Number of lots *l* of raw material $m \in \mathbf{W}$ at period *t*
Z_{pelt}	Process design variable for each product *p* of lot *l* assigned to processing unit *e* at period *t*

3.5.1.1. Constraints

$$\sigma_{ml} L_{mlt} = -\sum_{k \in \mathbf{K}_m} \nu_{km} B_{klt} \quad \forall p \in \mathbf{P}, m \in \mathbf{W}_p, l \in \mathbf{L}_m, t \in \mathbf{H} \tag{3.1}$$

$$\sum_{e \in \mathbf{E}_m} Y_{plet} \leq L_{mlt} \leq \gamma_{mt} \sum_{e \in \mathbf{E}_m} Y_{plet} \quad \forall p \in \mathbf{P}, m \in \mathbf{W}_p, l \in \mathbf{L}, t \in \mathbf{H} \tag{3.2}$$

$$Y_{plet} + Y_{pl'et'} \leq 1 \quad \forall p \in \mathbf{P}, e \in \mathbf{E}_p, l, l' \in \mathbf{L}_m : l' > l, t \in \mathbf{H}, t' = \{0 \dots t\} \tag{3.3}$$

$$R_{mlt} = \left(\mu_m^{initial}|_{t=0}, \; R_{m,t-1}|_{t>0}\right) + (\sigma_{ml} L_{mlt})|_{m \in \mathbf{W}} + \sum_{k \in \mathbf{K}_m} \nu_{km} B_{klt} - D_{mlt}|_{m \in \mathbf{P}} - W_{mlt}|_{m \in \mathbf{P^U}, t=\theta_i^F} \quad \forall m \in \mathbf{M}, l \in \mathbf{L}, i \in \mathbf{I}, t \in \mathbf{H} \tag{3.4}$$

$$0 \leq \sum_{l \in \mathbf{L}} R_{mlt} \leq \mu_m^{max} \quad \forall m \in \mathbf{M}, t \in \mathbf{H} \tag{3.5}$$

$$R_{ml}|_{t=\theta_i^F} = 0 \quad \forall m \in \mathbf{P^U}, l \in \mathbf{L}, i \in \mathbf{I}, t \in \mathbf{H} \tag{3.6}$$

$$\sum_{l \in \mathbf{L}} D_{mlt} = \omega_{mt} \quad \forall m \in \mathbf{P}, t \in \mathbf{H} \tag{3.7}$$

$$D_{mlt} = 0 \quad \forall m \in \mathbf{M} \backslash \mathbf{P}, l \in \mathbf{L}, t \in \mathbf{H} \tag{3.8}$$

$$\beta_{ke}^{min} N_{klt} \leq B_{klt} \leq \beta_{ke}^{max} N_{klt} \quad \forall e \in \mathbf{E}, k \in \mathbf{K}_e, l \in \mathbf{L}, t \in \mathbf{H} \tag{3.9}$$

$$Y_{plet} \leq B_{klt} \leq bigM Y_{plet} \quad \forall p \in \mathbf{P}, e \in \mathbf{E}, k \in \mathbf{K}_e, l \in \mathbf{L}, t \in \mathbf{H} \tag{3.10}$$

$$\sum_{l \in \mathbf{L}} \sum_{k \in \mathbf{K}_e^C} B_{klt}\, \bar{\tau}_{ke}^{var} + \sum_{l \in \mathbf{L}} \sum_{p \in \mathbf{P}^C} Y_{plet}\, \tau^{chg} - \tau^{chg} + F_e \leq \delta_e^{init}\, \tau \quad \forall e \in \mathbf{E}, t \in \mathbf{H} \tag{3.11}$$

$$\sum_{l \in \mathbf{L}} \sum_{k \in \mathbf{K}_e^U} B_{klt}\, \bar{\tau}_{ke}^{var} + \sum_{l \in \mathbf{L}} \sum_{p \in \mathbf{P}^U} Y_{plet}\, \tau^{chg} - \tau^{chg} \leq F_e + \sum_{t\prime=0}^{t-1} A_{et\prime}\tau + A_{et}(\tau - \hat{\tau}_e) \quad \forall e \in \mathbf{E}, t \in \mathbf{H} \tag{3.12}$$

$$Z_{plet} \geq Y_{plet} - Y_{ple,t-1} \quad \forall e \in \mathbf{E}, p \in \mathbf{P}_e, l \in \mathbf{L}, t \in \mathbf{H} \tag{3.13}$$

$$\sum_{t \in \mathbf{H}} Z_{plet} \leq 1 \quad \forall e \in \mathbf{E}, p \in \mathbf{P}_e, l \in \mathbf{L}, t \in \mathbf{H} \tag{3.14}$$

$$\begin{aligned}
R_{mlt} &\in \mathbb{R}_+ \quad \forall m \in \mathbf{M}, t \in \mathbf{H} \\
B_{klt} &\in \mathbb{R}_+ \quad \forall k \in \mathbf{K}, t \in \mathbf{H} \\
W_{mlt} &\in \mathbb{R}_+ \quad \forall m \in \mathbf{P^U}, t \in \mathbf{H} \\
D_{mlt} &\in \mathbb{R}_+ \quad \forall m \in \mathbf{P}, t \in \mathbf{H} \\
F_e &\in \mathbb{R}_+ \quad \forall p \in \mathbf{P^C}, e \in \mathbf{E} \\
N_{klt} &\in \mathbb{Z}_+ \quad \forall k \in \mathbf{K}, t \in \mathbf{H} \\
L_{mlt} &\in \mathbb{Z}_+ \quad \forall m \in \mathbf{W}, l \in \mathbf{L}_w, t \in \mathbf{H} \\
Y_{plet} &\in \{0,1\} \quad \forall p \in \mathbf{P}, e \in \mathbf{E}, t \in \mathbf{H} \\
A_{et} &\in \mathbb{Z}_+ \quad \forall e \in \mathbf{E}, t \in \mathbf{H} \\
Z_{plet} &\in \mathbb{Z}_+ \quad \forall p \in \mathbf{P}, e \in \mathbf{E}, t \in \mathbf{H}
\end{aligned} \tag{3.15}$$

Constraints (3.1) to (3.3) are used to model the lot-size and scale-up decisions based on the starting raw material of each final product *p*. Constraint (3.1) guarantees that the total amount available of raw material $m \in \mathbf{W}$ of lot *l* at each time period is equal to the total amount consumed by the respective tasks $k \in K_m$ of lot *l*. The parameters σ_{ml} on the left hand side of this constraint represent the lot-sizes of lot *l* for each raw material $m \in \mathbf{W}$, and the ν_{km} parameters on the right hand side take a negative value corresponding to the consumption rate of each task *k* and raw material *m*. Constraints (3.2) bound the number of lots of each lot-size *l* (L_{mlt}) to a given maximum value (γ_{mt}) for each starting raw material *m* associated with final product *p* ($m \in \mathbf{W}_p$) and period *t*. These constraints also guarantee that the number of lots will be zero if no product *p* of lot *l* is assigned to processing unit *e,* at period *t* (i.e. $Y_{plet} = 0$). Finally, constraints (3.3) model the scale-up decisions, by ensuring that the size of the lots never decreases during the planning horizon.

The excess resource balances are defined by constraints (3.4) in which the continuous variables R_{mlt} denote the material availability over time, for each material *m* of lot *l*. The parameters $\mu_m^{initial}$ represent the initial material availability for each material *m* (being 0 for final products and intermediaries). The second term of constraints (3.4) is activated only for raw materials, and it defines the starting raw material quantity, that is limited by the given lot-sizes (σ_{ml}). The total amount produced or consumed by each task is defined by the third term of these constraints in which

the parameters ν_{km} denote the proportion of material that is consumed (negative values) or produced (positive values) during the execution of the task.

This modelling approach has been introduced by Pantelides (1994). The continuous variables D_{mlt} define the amount of material delivered in each period, being 0 for all materials except final products ($m \in \mathbf{P}$). The last term will be activated only for products under development, and it corresponds to the leftovers of the final product, at the end of each clinical trial phase *i* (to be considered as wastage).

Constraints (3.5) define the excess resource capacity for each material and time interval, bounded by the given maximum materials availability μ_m^{max}. Furthermore, since the excess amount of final products under development at the end of each clinical trial phase must be discarded and cannot be used in the following periods, expression (3.6) is introduced to ensure that the material availability of these products is 0 at the end of each clinical trial phase.

Constraints (3.7) define the production requirements to meet the given demand (ω_{mt}), and expression (3.8) guarantees that only final products can be delivered.

Constraints (3.9) ensure that the total amount of material processed (B_{klt}) is bounded by the minimum and maximum processing unit capacities (β_{ke}^{min} / β_{ke}^{max}). The integer variable N_{klt} is defined as the number of instances (batches) of task *k*, for lot *l,* in period *t*.

Constraints (3.10) are very similar to constraints (3.2) defined earlier, but even though they are necessary, since constraints (3.2) apply only for the starting raw materials m ($m \in \mathbf{W}$). These additional constraints (3.10) are then used to activate the decision variables B_{klt} (total amount processed) associated to all tasks k ($k \in \mathbf{K}_e$), and to force those variables to be 0 if no product p of lot l is assigned to processing unit e at period t (i.e. $Y_{plet} = 0$). The $bigM$ represents a very large number (in relative terms), and Y_{plet} are the binary variables for process activation.

Constraints (3.11) and (3.12) define the production capacity, expressed in the total time availability for processing unit e and period t. Given that only capacity extensions for products under development are allowable in this formulation, a distinction must be done regarding the two types of products. Thus, constraints (3.11) denote the production capacity for products in commercialization, and constraints (3.12) for products under development. The first summation in (3.11) represents the total time required for the execution of tasks *k*, in which the coefficient $\bar{\tau}_{ke}^{var}$ is known and denotes the time required per unit of processed material. The second summation defines the changeover times associated to product and lot changing. Parameter τ^{chg} represents the changeover time. A third term (τ^{chg}) is added to constraints (3.11) in order to ensure that the number of changeovers is equal to the number of products minus one. This is needed to prevent an overestimation of the changeover times across adjacent periods in which the last product of the previous period is equal to the first product of the following period (Grossmann, 2007). The last term (F_e) expresses the capacity of each processing unit e unused by the products in commercialization. This free capacity will be used as available capacity for the products under development in

constraints (3.12). The right hand side of these constraints is the total available capacity of each processing unit *e,* in each period. The parameters δ_e^{init} and τ are given, and denote respectively the number of processing units *e* initially available at the plant and the length of each period *t*. In constraints (3.12), the left hand side is equal to constraints (3.11), except for the decision variables F_e, that, in this case, are in the right hand side, as they reflect the available capacity for the production of the under development products. However, because this available capacity is very limited, it is likely that some adjustments to the process design will be needed, and some capacity extensions performed. Accordingly, integer variables A_{et} are introduced in constraints (3.12), to determine the additional amount of capacity (expressed in additional time) required for the production of each product p ($p \in \mathbf{P^U}$) in processing unit *e*. Thus, the second term in the right hand side of these constraints refers to the total capacity added in previous periods (t = 0,…,t-1). This term guarantees that, if an increase in capacity occurs, the new processing units added to the plant will be available during the following periods until the end of the planning horizon. Finally, the last term of these constraints denotes the capacity extensions to be performed in period *t*, also reflecting the time required for the installation and commissioning of the added units before they are ready to start operating ($\hat{\tau}_e$).

Constraints (3.13) and (3.14) are process design constraints needed to ensure that, after a processing unit has been selected for a given process, it cannot leave that process in a given period and be later assigned again to the same process (i.e., in a period ahead). Finally, expressions (3.15) are used to define the domain of the variables.

3.5.1.2. Objective Function

As referred above, and in order to reflect in the model the main concerns of the company, we have considered as objective function (eq.(3.16)) the maximization of the Net Present Value (NPV) of the operations related to these projects. This measure depends on the income from sales over the planning horizon (INCO) minus the operational costs (OC), storage costs (SC), disposal costs for wasted final products (WC), changeover costs (COC), scale-up costs (LC), and investment costs (IC) (costs associated with capacity extension):

$$\max NPV = INCO - OC - SC - WC - COC - LC - IC \tag{3.16}$$

Considering the discount factor (d_t) given by expression (3.17), where r is the interest rate and t the period (Bagajewicz, 2008), each term of the objective function (3.16) can be described individually as presented below.

$$d_t = \frac{1}{(1+r)^t} \quad \forall\, t \in \mathbf{H} \tag{3.17}$$

The income over the planning horizon results from the final product sales, and is given by expression (3.16)a, where π_m denotes the given sale prices for each material *m.*

$$INCO = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{m\in\mathbf{P}} \sum_{t\in\mathbf{H}} (\pi_m D_{mlt}) \qquad (3.16)\text{a}$$

The operational costs are associated with each task *k,* and are given by expression (3.16)b, where $\alpha_k^{oper.}$ is the operational cost of task *k.*

$$OC = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{k\in\mathbf{K}_e} \sum_{t\in\mathbf{H}} \left(\alpha_k^{oper.} N_{klt}\right) \qquad (3.16)\text{b}$$

Storage costs are also considered in this model, and they are given by eq. (3.16)c, where $\alpha_m^{stor.}$ represents the holding costs for each material *m*.

$$SC = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{m\in\mathbf{M}} \sum_{t\in\mathbf{H}} (\alpha_m^{stor.} R_{mlt}) \qquad (3.16)\text{c}$$

The costs associated to the disposal of unused final products under development (waste) are given by expression (3.16)d.

$$WC = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{m\in\mathbf{P^U}} \sum_{t\in\mathbf{H}} (\alpha_m^{waste} W_{mlt}) \qquad (3.16)\text{d}$$

The changeover costs are given by eq. (3.16)e, where the given parameters α_e^{chg} denote the changeover costs associated to each processing unit *e*.

$$COC = \sum_{t\in\mathbf{H}} d_t \sum_{l\in\mathbf{L}} \sum_{e\in\mathbf{E}} \sum_{p\in\mathbf{P}} \sum_{t\in\mathbf{H}} \left(\alpha_e^{chg} Y_{plet}\right) \qquad (3.16)\text{e}$$

The costs associated to the scale-ups are given by eq. (3.16)f, where $\alpha_{ml}^{lot\ size}$ denotes the cost associated to the selection of the lot size *l* for the starting raw material *m*.

$$LC = \sum_{t\in\mathbf{H}} d_t \sum_{m\in\mathbf{W}} \sum_{l\in\mathbf{L}_w} \sum_{t\in\mathbf{H}} \left(\alpha_{ml}^{lot\ size} L_{mlt}\right) \qquad (3.16)\text{f}$$

Finally, if a capacity expansion occurs ($A_{et} > 0$), an investment cost must be considered for each new processing unit that is added to the plant. These costs are given by eq. (3.16)g, where the parameters $\alpha_e^{invest.}$ are the investment costs associated to each new processing unit *e* added to the plant.

$$IC = \sum_{t\in\mathbf{H}} d_t \sum_{e\in\mathbf{E}} \sum_{t\in\mathbf{H}} (\alpha_e^{invest.} A_{et}) \qquad (3.16)\text{g}$$

3.6. Mathematical Results and Discussion

3.6.1. Case description

To validate the proposed framework and demonstrate its applicability, a case was designed based on a real problem of the chemical-pharmaceutical industry. In this case, the product portfolio is composed by 3 new products (PA, PB, and PC) entering the product development phase, and by 2 products (PD and PE) already in commercialization. A planning horizon of 5 years is considered, discretized into 10 periods of 6 months each (4032 hours for a plant, operating 24 hours a day and 7 days a week). The demand forecast profiles for the entire planning horizon and for each product are presented in Figure 3.5. To accommodate the three phases for the clinical trials, the planning horizon is divided, with 1.5 years to conduct each of the clinical trials phases I and II, and with 2 years for clinical trial phase III (see Figure 3.5).

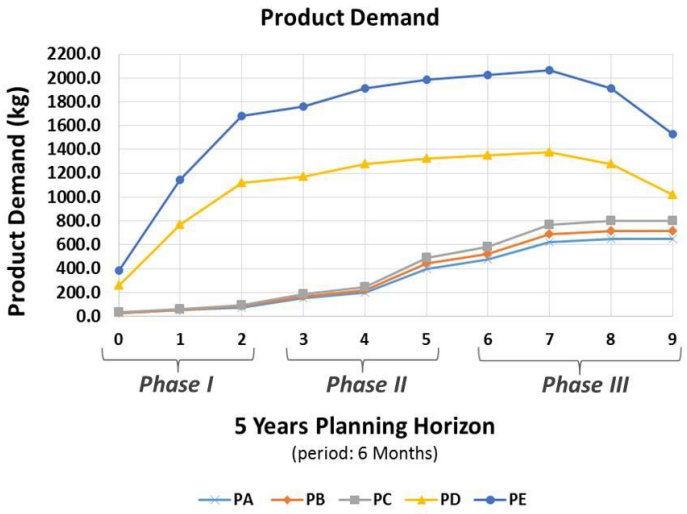


Figure 3.5 Demand profile for products under development (PA, PB and PC) and products already in commercialization (PD and PE) (Sundaramoorthy et al., 2012)

All products follow a similar production recipe in which the task sequence, unit suitability, reaction yields, and processing times are clearly identified (see Figure 3.6). All processes are composed by 3 aggregate tasks that can be processed in 3 possible unit types ({R1, R2, R3}, {F1, F2, F3}, and {D1, D2, D3}) with different capacities, and different operational and investment costs (see Figure 3.7). These tasks have a variable duration (expressed in hour/kg) that is proportional to the batch size. Moreover, each product can only be produced in pre-determined lot-sizes, with four different lot-sizes defined for each product.

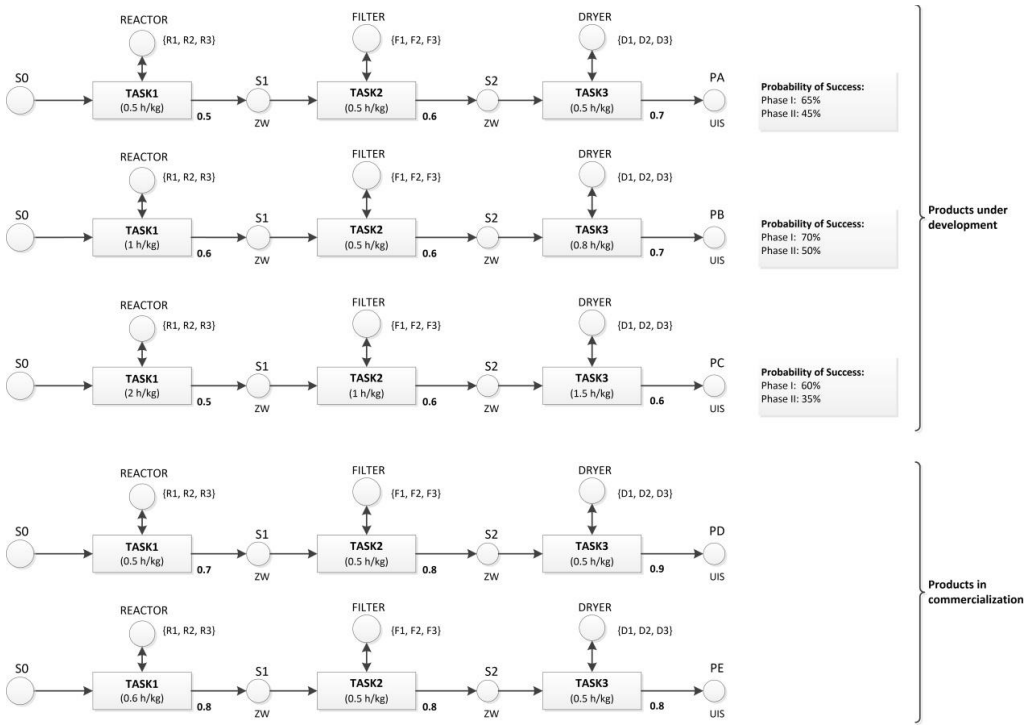


Figure 3.6 Product recipes (task processing times and process yields) and probabilities of success for the products under development and for the products already in commercialization.

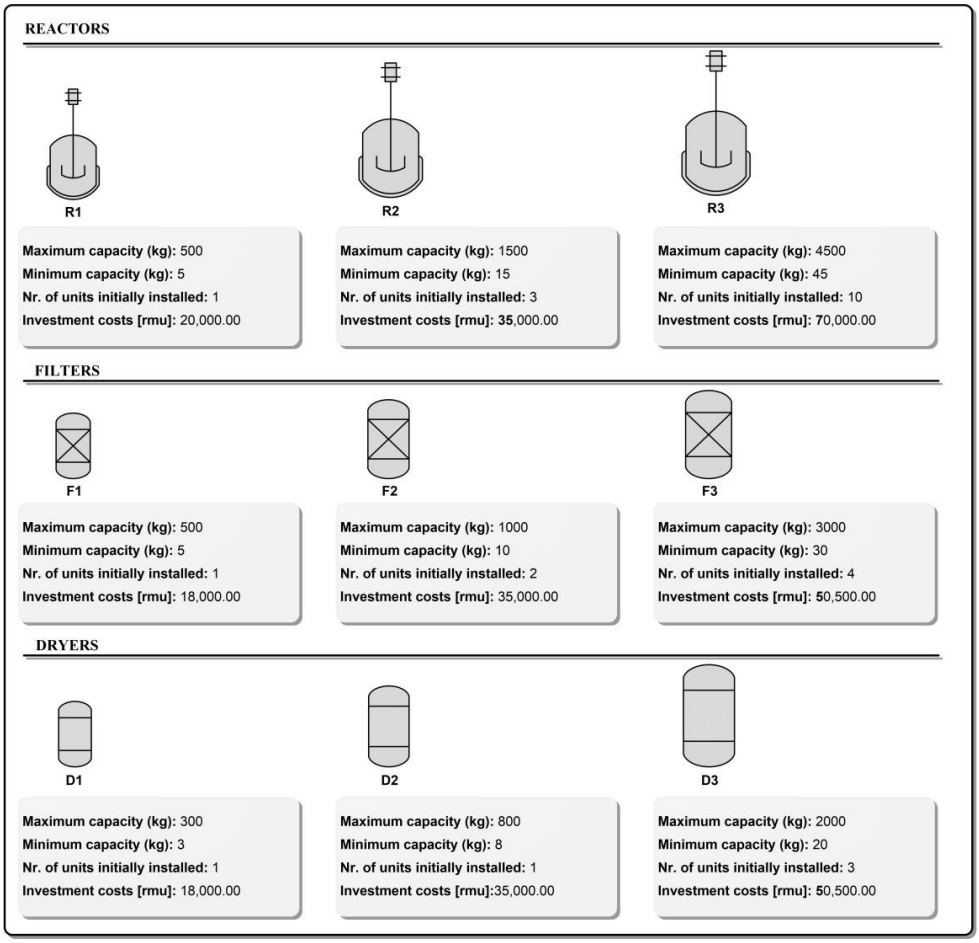


Figure 3.7 Processing unit types and their maximum and minimum capacities.

To reflect the uncertainty of product demand, normal distributions are used with values, per period, for the mean and standard deviations, derived from the profiles presented in Figure 3.5. We have considered a standard deviation of 30% for the products under development, and 10% for the products in commercialization, since less demand variability is expected in this case. On the other hand, to capture the uncertainty associated to the clinical trials (pass/fail outcomes), Bernoulli distributions are used, considering the success probabilities depicted in Figure 3.6, and based on the available information from the literature (Fisher et al., 2015).

3.6.2. Computational results

The MILP model was implemented using IBM ILOG CPLEX Optimization studio, version 12.5.1, running on an Intel Xeon at 3.33 GHz machine with 24 GB of RAM. As stopping criterion, we considered a time limit of 3600 seconds, and an *integrality gap* of 5%. For the simulation component (MCS), an iterative model was also implemented in ILOG/CPLEX, and 1000 iterations were performed by randomly generating the uncertainty parameters from given probability distributions (normal and Bernoulli distributions). The number of iterations was defined based on a previous sensitivity analysis.

For each iteration, a solution was found and the frequency of occurrence for each decision variable was determined and analysed. The MCS for the 1000 iterations took a total of 36 hours to be completed, with an average run time, for each iteration, of 129.35 seconds. The *integrality gap* ranges from a minimum of 1.43% to a maximum of 5.0% (according to the stopping criterion referred above). The main computational statistics are described in Table 3.1.

Table 3.1 Computational statistics

binary variables	integer variables	continuous variables	constraints	B&B nodes*	optimality gap (%)*	CPU time (seconds)*
1,800	3,890	3,554	29,160	10,356.29	3.8	129.35

* Average values for the 1000 iterations.

3.6.2.1. NPV analysis

The results obtained are presented in Figure 3.8, with the NPV histogram and the associated probability distribution. The resulting histogram presents a slightly skewed right pattern, due to the fact that the NPV highest values occur in the instances in which all products under development successfully pass all clinical trial phases, this fact having a very low frequency of occurrence, as it is highly unlikely to happen.

The maximum NPV value obtained was 1.79×10^7 relative monetary units *(rmu);* the minimum value was 1.28×10^7 *rmu* and the average NPV was 1.50×10^7 *rmu*. The variation between the average and the minimum values is about 14%, which may be more or less penalizing for the company, depending on the particular context, the main established goals, and the risk aversion of the decision makers.

On the other hand, the optimal profit for the deterministic reference case, which is based on the forecast values illustrated in Figure 3.5 was 1.69×10^7 *rmu*. According to Figure 3.8, the frequency of

occurrence of this value is just 3 in 1000 iterations, and the probability of the profit to be below this value is about 98% (see Figure 3.8), this meaning that the deterministic case is very unlikely to occur. These results clearly show that the decision-making process for a 5 years capacity planning entails a considerable risk if we only consider a deterministic analysis.

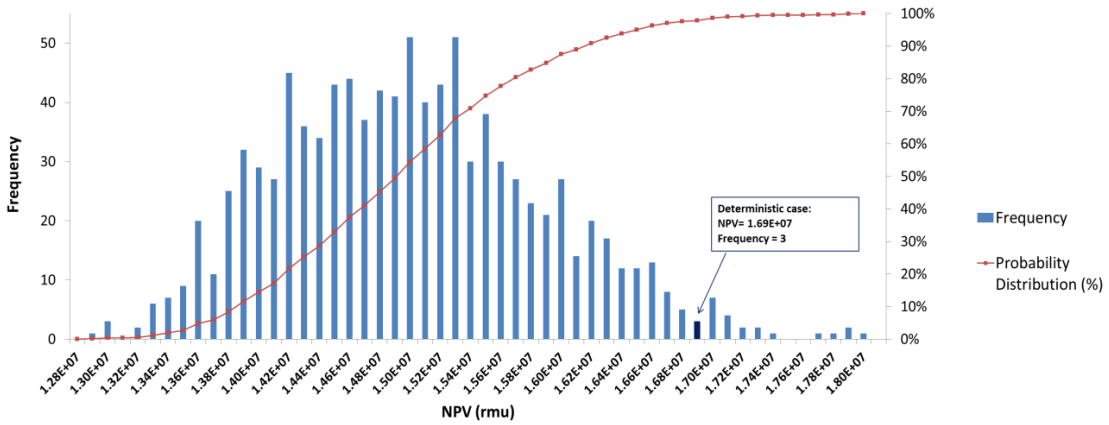


Figure 3.8 NPV histogram and associated probability distribution.

3.6.2.2. Scale-up analysis

The determination of the lot-sizes to be produced, and of the scale-ups to be performed are very important decisions in the chemical-pharmaceutical industry. From a strict cost point of view, the production of larger, fewer lots is more desirable, as demonstrated in (Moniz et al., 2014b). Here, the results show that the most frequently selected lot-sizes and scale-ups over the entire planning horizon are in accordance with the previous statement, since there is a clear preference for single lots, particularly for the under development products. Exceptions occur when the demand is very high. Since no backlogs are allowed, when demand is high the model is forced to select several lots of a certain size in order to completely meet the product demand.

The histograms in Figure 3.10 and in Figure 3.11 are for the products under development, and for the products in commercialization, respectively. These histograms only present the lot-sizes that are more frequently selected by the model in each period. For example, for product PA, at period t=0, all the lot-sizes selected by the model are depicted in Figure 3.9. However, only the most frequently selected (1L3_200) lot-size was picked for the histogram in Figure 3.10a). This procedure was performed for all products and periods.

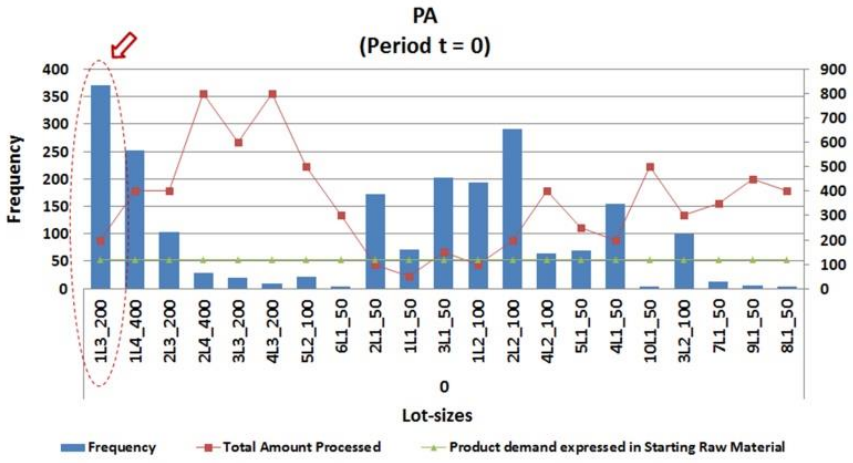


Figure 3.9 Selected lot-sizes for product PA, at period t=0.

When analysing the histograms of both types of products, we can notice that in the first case (products under development), there is a considerable decrease in the frequency values in each clinical trial phase, this being a direct consequence of the pass/fail probabilities associated to the products. For the products in commercialization, this decrease does not occur due to their much more stable demand. According to Figure 3.10, the most frequently selected lot-sizes for the products under development are: lot 3 and lot 4, for product PA; lot 1 and lot 4, for product PB; and finally, lot 1, lot 2, lot 3 and lot 4, for product PC. These values correspond to one scale-up for product PA and product PB, and three scale-ups for product PC, over the planning horizon. In all the three products, we can observe that the scale-ups are closely related to the clinical trial phases, even if this is more evident in the case of product PC, because of the higher values of the product demand. In that sense, for product PA, it seems reasonable to consider lot 3 for clinical trial phase I, and lot 4 for the other two clinical trial phases. For product PB, it is clear that the most suitable lot for phase I is lot 1, and lot 4 for the last two clinical trials phases. Finally, for product PC, it seems reasonable to consider lot 1 for clinical trial phase I, lot 2 and 3 for clinical trial phase II, and lot 4 for clinical trial phase III. On the other hand, for products in commercialization (PD, and PE), the larger lot (lot 4) is the most frequently selected, due to the larger and more stable values for the product demand. This is particularly evident for product PE that presents a higher product demand for almost the entire planning horizon. It is worth to notice that the product demand and the total amount processed (depicted in Figure 3.10 and in Figure 3.11) correspond to the starting raw materials associated to each final product, and derived from the forecasted values presented in Figure 3.5 (considering the associated production yields).

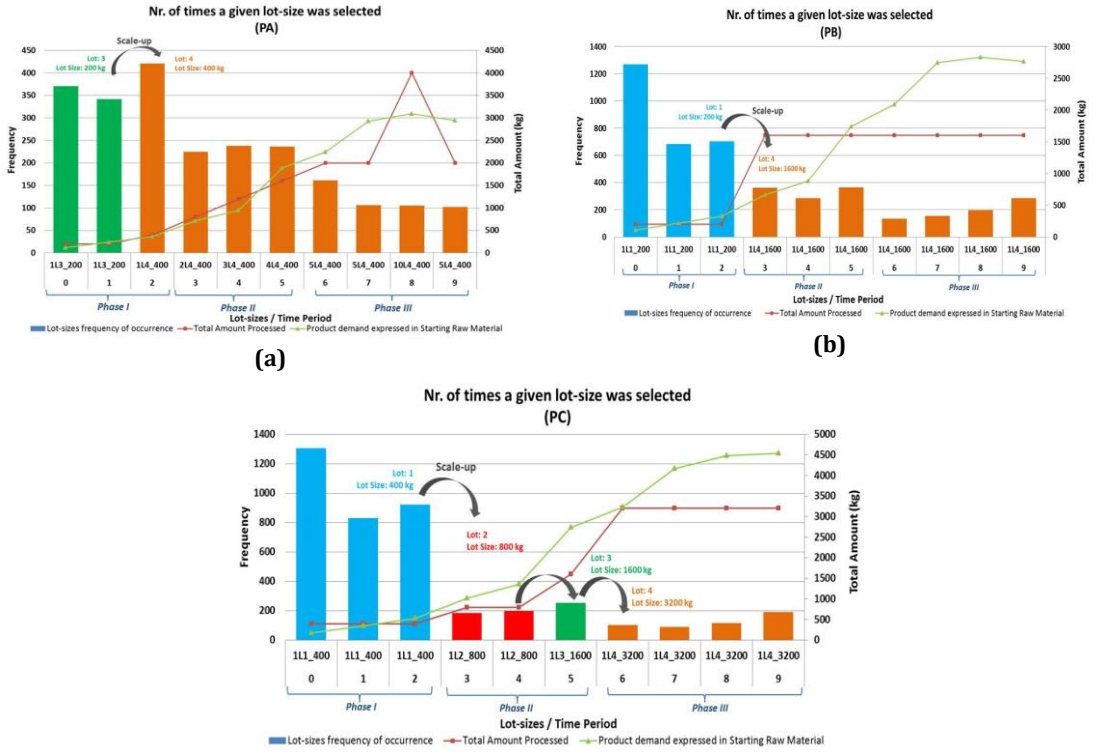


Figure 3.10 Lot-size and scale-up decisions for products under development: (a) product PA, (b) product PB, and (c) product PC.

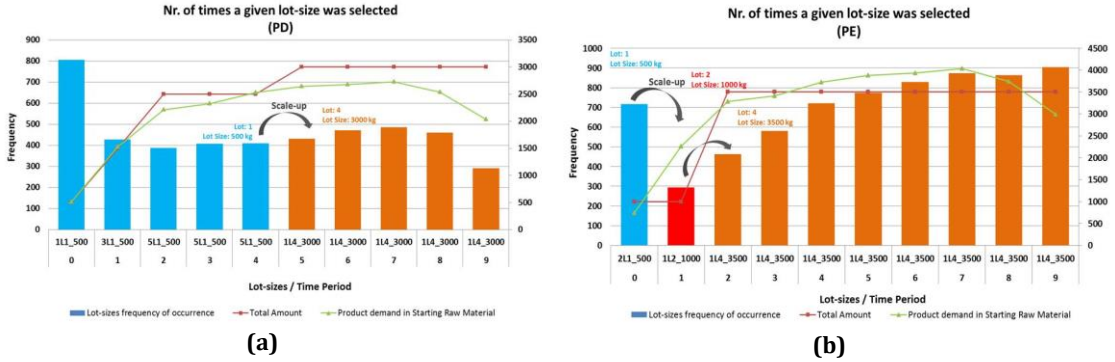


Figure 3.11 Lot-size and scale-up decisions for products already in commercialization: (a) product PD, and (b) product PE.

Finally, the most likely process design configurations for each product and clinical trial / planning period were determined. In the next section, the trade-offs between process design configuration and scale-ups are analysed.

3.6.2.3. Process design and scale-up analysis

These results also allow us to identify the sets of processing units associated with the lot-sizes that have been selected with higher probabilities. They are presented as histograms in Figure 3.12 (a1, b1, c1), and in Figure 3.13 (d1, e1), for the products under development and in commercialization, respectively. In this case, the histograms were obtained by considering the three or four most frequently selected process configurations.

We can also see that, when simultaneously considering process design and lot-size configuration, the most selected process designs seem to lead to more scale-ups (2 or 3) than in the previous analysis (with just scale-ups). This seems to show that the model tends to favor the process design stability over scale-ups and lot size increases. This is an interesting result, satisfying some of the main goals of the problem, such as the enhancement of process stability, the minimization of process changes, and the preservation of its life cycle.

However, based on these results, it is not possible to guarantee that the most selected process configurations in each period / clinical trial phase, are obtained in the same iteration of the simulation framework. Thus, in order to minimize possible misinterpretations of the results, a robustness measure for each process design configuration was developed. This measure is computed for the three or four process designs more frequently selected in each period and reflects the percentage in which each process is repeated in more than two periods in the same iteration. These results are illustrated in Figure 3.12 (a2, b2, c2) for products under development, and in Figure 3.13 (d2, e2) for products in commercialization.

A combined analysis of the two results (frequency histograms and robustness charts) can be used to support the decision-making process in a more reliable way. Thus, from this analysis, it seems plausible to consider that the process design configuration {R1, F1, D1} is the most suitable for product PA, with one scale-up at the end of the clinical trials phase I, from lot 2 (100 kg) to lot 4 (400 kg). Similarly, for product PB, the process design configuration {R1, F1, D1} seems to be the most adequate decision for clinical trials phases I and II, and {R2, F2, D1} for the last clinical trial phase. Also in this case, one scale-up occurs, but at the end of clinical trials phase II, from lot 1 (200 kg) to lot 4 (1600 kg). Finally, for product PC, it seems reasonable to consider that the most suitable process design configuration is {R1, F1, D1} for clinical trials phases I and II, and {R3, F2, D2} for clinical trials phase III. Again, one scale-up is expected at the end of clinical trials phase II, from lot 1 (400 kg) to lot 4 (3200 kg).

A similar analysis is made for both products in commercialization (PD and PE). For product PD, the best process design configuration seems to be {R1, F1, D1}, associated with lot-size 1 (500 kg) for the first two periods (corresponding to the first year), and {R3, F3, D3}, associated with lot-size 4 (3000 kg) for the rest of the planning horizon. For product PE, the most frequently selected and robust process design configuration is {R2, F1, D1} for the entire planning horizon, with one scale-up at the end of time period 3 (corresponding to the first 2 years), from lot 2 (1000 kg) to lot 4 (3500 kg).

Additionally, from the analysis of the robustness charts, we can see that in most of the cases, a change in the lot size is accompanied by a change in the process design configuration for higher capacity processing units. This means that lower capacity units tend to be chosen in the lower product demand periods / early stages of development, and the higher capacity units are more frequently selected in the higher product demand periods / last stages of development. Moreover, the higher capacity processing units seem to be more frequently chosen for the products already in commercialization. In that sense, the model seems to achieve a good trade-off between the capacity of processing units, and both product demand and process stability. Moreover, it is clear from the results obtained for the under-development products, that process design configurations and scale-ups are strongly connected to the success of the clinical trials, this showing the relevance of this analysis, that provides reliable information to boost sooner decisions with minimal risk.

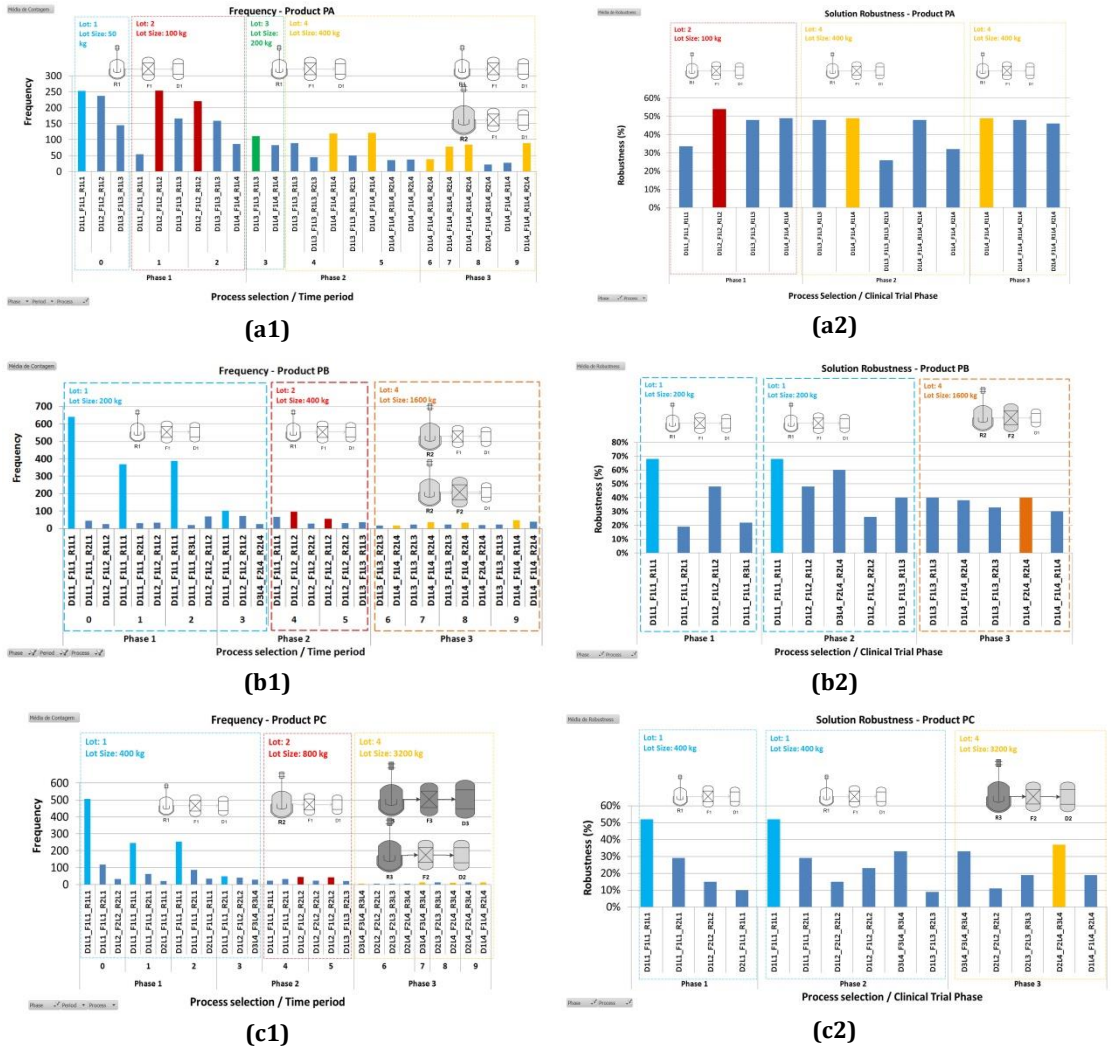


Figure 3.12 Process design selection and solution robustness for the products under development.

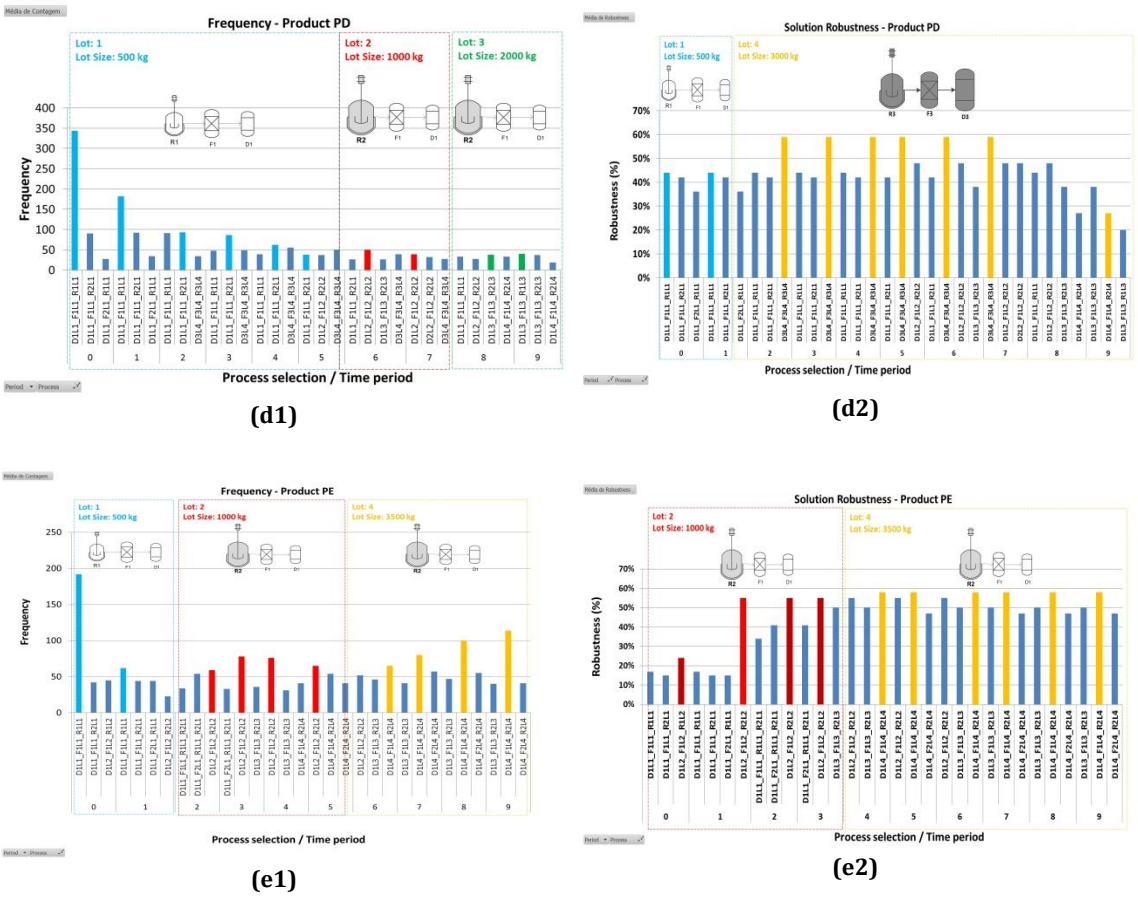


Figure 3.13 Process design selection and solution robustness for the products in commercialization.

When comparing these results to the deterministic case, for the products under development (see Table 3.2), we can see that in the earlier stages of development, the process design configurations are very similar (with the exception of product PB). This can be explained by the fact that one of the initial assumptions in this work was that all the three products enter clinical trial phase I at the same time, and also by the low levels of product demand and high capacity availability at this phase. However, moving forward through the time horizon, to the clinical trial phases II and III, the differences become significant in terms of capacity utilization. It is clear that, in the deterministic case, the decisions tend to benefit higher investments in capacity utilization. For example, in phase III, in almost all cases, the model selects two or more processing units of the same type in the same period. This reveals the conservative nature of the model that, in order not to fail any delivery, tends to oversize both the capacity utilization and the resource allocation. Additionally, according to the previous NPV analysis, the "deterministic case" is very unlikely to occur, this meaning that this high investment in capacity utilization is most likely not to be needed.

In this context, the approach proposed in this work can provide valuable and robust information to support the medium and long-term decision-making process, in what concerns production planning and process design configurations, for new drug development. Even if this approach does not give a unique specific solution to the addressed planning problem, it provides robust guidelines for effective decision making, based on several possible solutions, and considering a highly stochastic

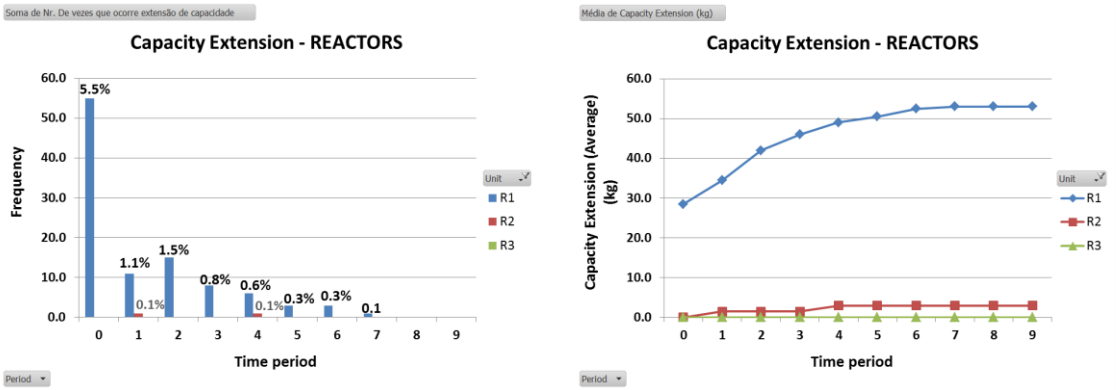
environment. It also supports the evaluation of the available solutions, considering the process design configurations and their maintenance throughout the entire life-cycle of the possible new commercial drugs.

Table 3.2 Deterministic process design results for the under-development products

	Product PA		Product PB		Product PC	
	t	Process	t	Process	t	Process
Phase I	0	D1L2_F1L2_R1L2	0	D1L4_F2L4_R1L4_R2L4	0	D1L1_F1L1_R1L1
	1	D1L2_F1L2_R1L2	1	D1L4_F3L4_R1L4	1	D1L1_F1L1_R1L1
	2	D1L2_F1L2_R1L2	2	-	2	D1L1_F1L1_R1L1
Phase II	3	D1L4_F1L4_R1L4	3	D2L4_F2L4_R1L4	3	D1L1_F1L1_R1L1_R2L1
	4	D1L4_F1L4_R1L4	4	D2L4_F2L4_R1L4	4	D2L1_F1L1_R1L1_R2L1
	5	D1L4_F1L4_R1L4_R2L4	5	D2L4_F1L4_F2L4_R1L4	5	D2L1_F2L1_R1L1_R2L1
Phase III	6	D1L4_F1L4_R1L4_R2L4_R3L4	6	D1L4_F1L4_F2L4_R1L4_R2L4	6	D2L1_F2L1_R1L1_R2L1
	7	D1L4_F1L4_R1L4_R2L4_R3L4	7	D1L4_F1L4_F2L4_R1L4_R2L4	7	D2L2_F2L2_R1L2_R3L2
	8	D1L4_F1L4_R1L4_R2L4_R3L4	8	D1L4_F1L4_F2L4_R1L4	8	D2L2_F2L2_R1L2_R2L2
	9	D1L4_F1L4_R1L4_R2L4	9	D1L4_F1L4_R1L4	9	D2L2_F2L2_R2L2

3.6.2.4. Capacity extensions and inventory analysis

In the case under analysis, the initial capacity appears to fit the production requirements, since capacity extensions over the entire planning horizon are negligible. In fact, the most significant capacity extensions occur for the *reactors*, particularly for unit R1. Figure 3.14 shows the histogram (a) and the average capacity extensions in kilograms (b) for the equipment type "reactor". The most substantial capacity extension occurs in the first period, with a probability of occurrence of just 5.5% in the 1000 iterations, this representing an average capacity increase, in the same period, of just 28.5 kg.



(a) **(b)**

Figure 3.14 Capacity extension for reactors: (a) frequency of occurrence of a capacity extension, and (b) capacity extension expressed in average of additional capacity in kg, over the 1000 iterations.

On the other hand, when analysing the inventory levels shown in Figure 3.15, we can see these values are not significant (except for the initial periods when more capacity is available), when compared to the average product demand values presented in Figure 3.5. The model not only minimizes the amount stored, but also maintains it relatively stable over the entire planning horizon, for all the

products (despite the increase in product demand over time). Note that for the products under development (PA, PB, and PC), the inventory drops to 0.0 kg at periods t=2, t=5, and t=9. This is due to the fact that the leftovers at the end of each clinical trial cannot be reused and therefore they are treated as waste and considered discarded. The average of the wastage levels, for each product under development, is shown in Figure 3.16.

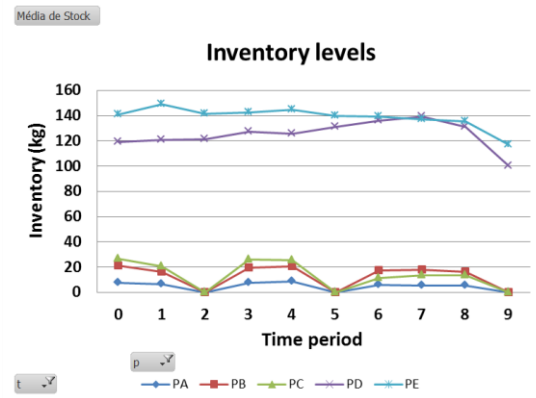


Figure 3.15 Average levels of inventory over the entire planning horizon, for each product.

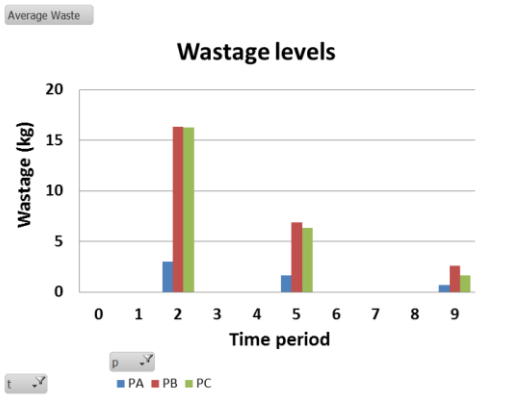


Figure 3.16 Wastage levels for the products under development, at the end of each clinical trial phase.

These results show that the model is handling well the trade-off between capacity investments and inventory requirements. Moreover, since the model minimizes both types of costs, in order to keep a relatively stable inventory level over the planning horizon, the additional capacity needs are fulfilled by the smallest and cheapest equipment (R1). In this way additional flexibility is added to the plant. Finally, the average values of wastage shown in Figure 3.16 are really not significant, in particular for periods 5 and 9, with values around 1% and less than 0.5% of the average amount delivered respectively, revealing an efficient resource utilization (this aspect deserving to be further explored in future work). Furthermore, according to Figure 3.16, the values of wastage are decreasing over the planning horizon, even if the amounts delivered are increasing (contrary to the inventory levels that remain relatively stable), this denoting a good wastage management by the model.

3.6.3. Two-step MCS framework Extension

In this section an improvement is proposed to the previously developed methodology, in order to include an additional important source of uncertainty: the uncertainty in processing times. This extension has a twofold goal: firstly, to assess the easiness of incorporation and solving simultaneously additional sources of uncertainty within the developed approach, and secondly to determine the impact of considering simultaneously the additional uncertainty in processing times.

The two-step MCS framework incorporating the additional source of uncertainty is depicted in Figure 3.17, with the dark grey box highlighting the contribution of this section to the original framework.

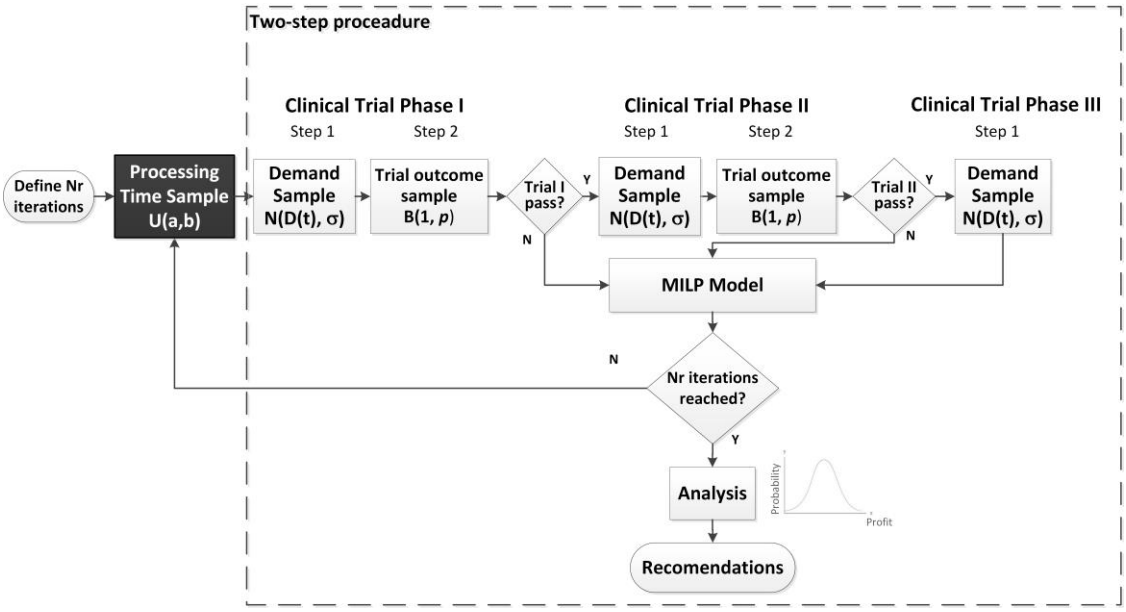


Figure 3.17 Two-step MCS framework extended.

As in the original framework, to model the variability in product demand and in the clinical trials, normal and Bernoulli distributions are considered respectively, while for the processing times variability, uniform distributions are considered. The uniform distribution has been widely used in the literature to capture the task processing times uncertainty as it is assumed to be a good approximation of its behaviour (Bassett et al., 1997; Subramanian et al., 2000; Chu et al., 2015a).

Similarly to the previous description, in the case of the products already in commercialization, a simple random sample is computed in each iteration, but in this case for both: the product demand in each period, and the processing time of each task. For the products under development, the simulation framework starts with the random generation of the processing time of each task, and then the two-step sampling procedure is executed as described previously (see section 3.4) for the random generation of the product demand and clinical trials outcomes.

3.6.3.1. Computational results

For the sake of comparison, the same illustrative example described earlier (section 3.6.1) including the respective parameter values are used here to validate the extended framework. Regarding the uniform distribution for the processing times, a symmetric deviation of ± 33% around the average values was assumed, for both types of products.

The MILP model and the MCS component were implemented using IBM ILOG CPLEX Optimization studio, version 12.6.0, and the results were obtained running the extended MCS framework (Figure 3.17) for 1000 iterations. The complete simulation took about 93 hours with an average run time for each iteration of 335.60 seconds, and an average *integrality gap* of 3.86%. As in the original case, the results (objective function and decision variables) are presented as histograms and probabilistic distributions.

Regarding the objective function, Figure 3.18 shows the values obtained for the NPV, with the maximum value for the NPV observed under uncertainty being 1.78 x 10^7 relative monetary units (rmu), with a minimum value of 1.27 x 10^7 rmu, and an average of 1.49 x 10^7 rmu. These values are very similar (slightly lower) to those obtained without considering uncertainty in processing times. Not only the NPV values, but also the slightly skewed right pattern of the histograms are identical (the differences are less than 1%).

This result is natural, since the major impact of uncertainty comes from the clinical trials "pass"/"fail" variability, leading to a further development of the product until its commercialization or to its abandonment, with the termination of the development process and the loss of all the investments made so far. Therefore, the effect of the additional uncertainty in processing times is almost unnoticed in the NPV values.

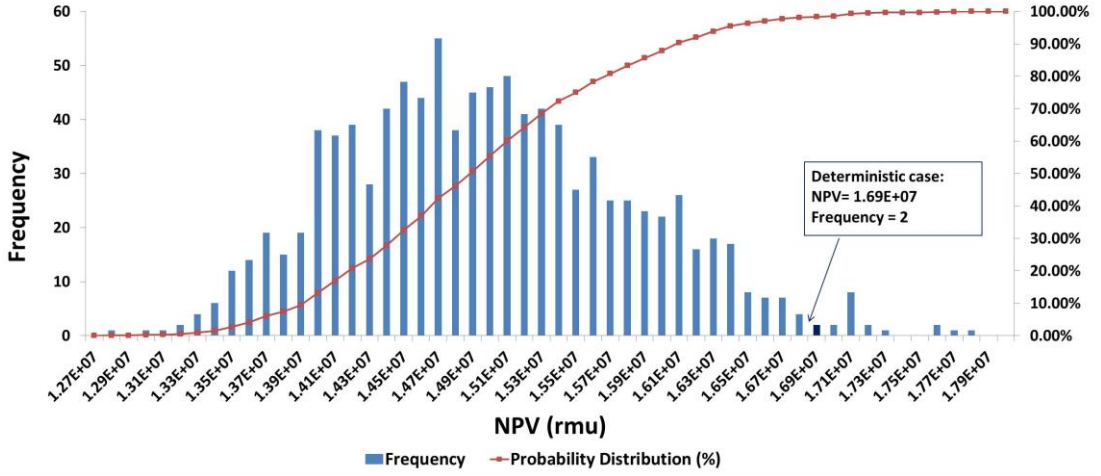


Figure 3.18 NPV histogram and probability distribution.

Nevertheless, regarding the process design, scale-up, and capacity extensions decisions, some relevant differences arise when considering the uncertainty in the processing times. Concerning the process design and scale-up results, the main difference occurs in the last periods of the planning horizon, with the selection of processing units with higher capacities in almost all the products considered. These results are particularly evident for the product PC (under development) as depicted in Figure 3.19.

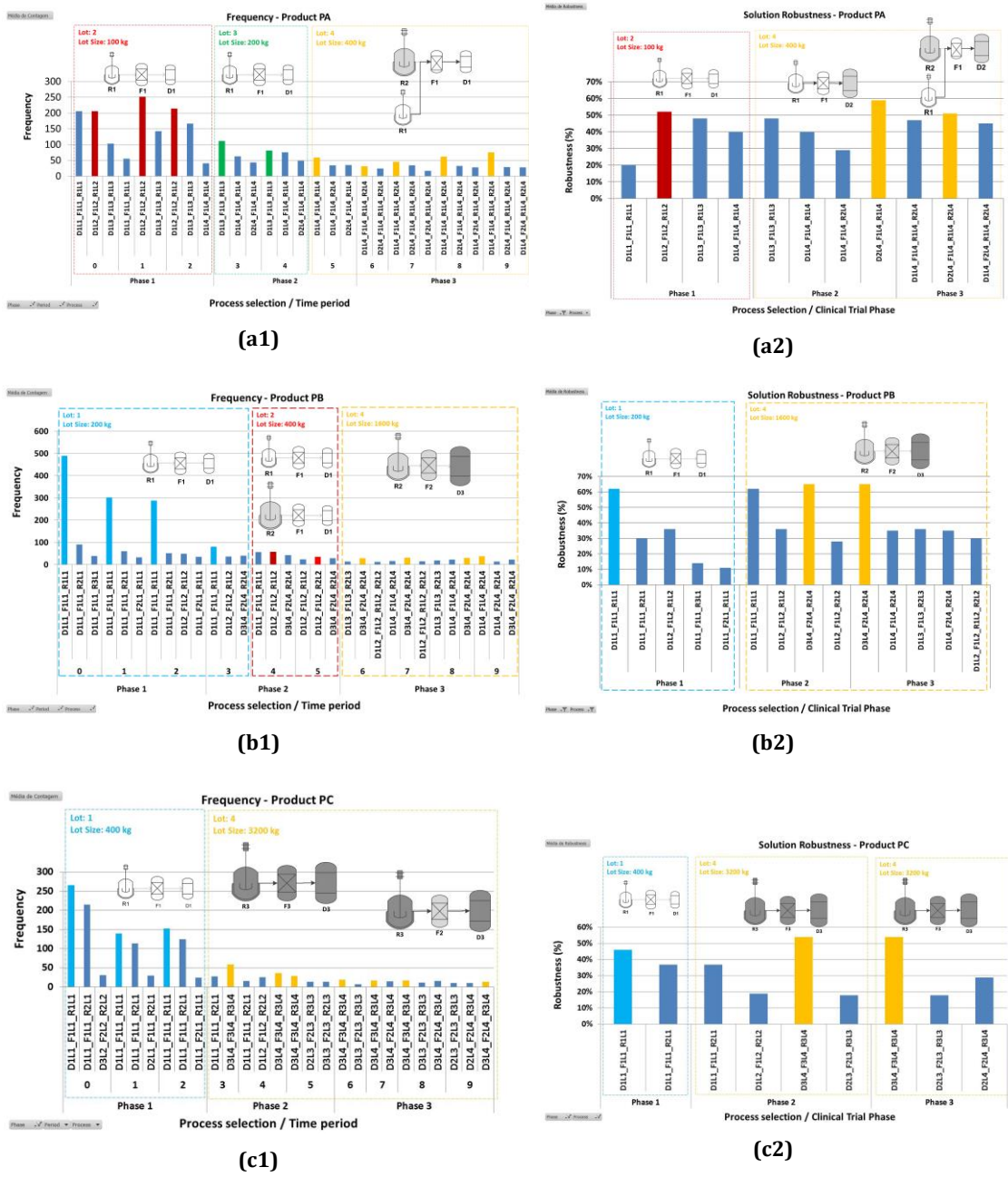


Figure 3.19 Results for the products under development including uncertainty in processing times: (a) process design selection; (b) solution robustness.

Figure 3.19 and Figure 3.20 present the most frequently selected set of processing units associated with lot-sizes, as well as the "solution robustness" as previously defined (see section 3.6.2.3), considering the additional uncertainty in processing times. Comparing these results with the previous ones obtained without considering the uncertainty on processing times (please refer to Figure 3.12 and Figure 3.13 in sub-section 3.6.2.3), we can state that when considering this additional uncertainty, scale-ups tend to occur earlier and associated with processing units of higher capacity. This seems to happen in almost every product, as it is the case for instance of product PC in which, a scale-up from lot-size L1 (400 kg) to L4 (3200 kg) occurs from clinical trial phase I to phase II, with the processing units also increasing in capacity from R1_F1_D1 to R3_F3_D3. When not considering

uncertainty in processing times, the combined analysis of frequency and robustness for product PC leads to the selection of lot-size L1 and processing units R1_F1_D1 for the clinical trial phase II. In this case, the equivalent scale-up will only occur from phase II to phase III (Figure 3.12 (c1) and (c2)).

In what concerns to the products already in commercialization, a similar analysis is found in the case of product PE. It is observed that, not only the scale-up from L2 to L4 occurs earlier, but also the equipment sizes increase in all processing units.

An exception seems to be the product PD, in which the analysis of the solution robustness depicted in Figure 3.20 (a2) indicates a scale-up later then its equivalent for the case that does not consider the uncertainty in processing times.

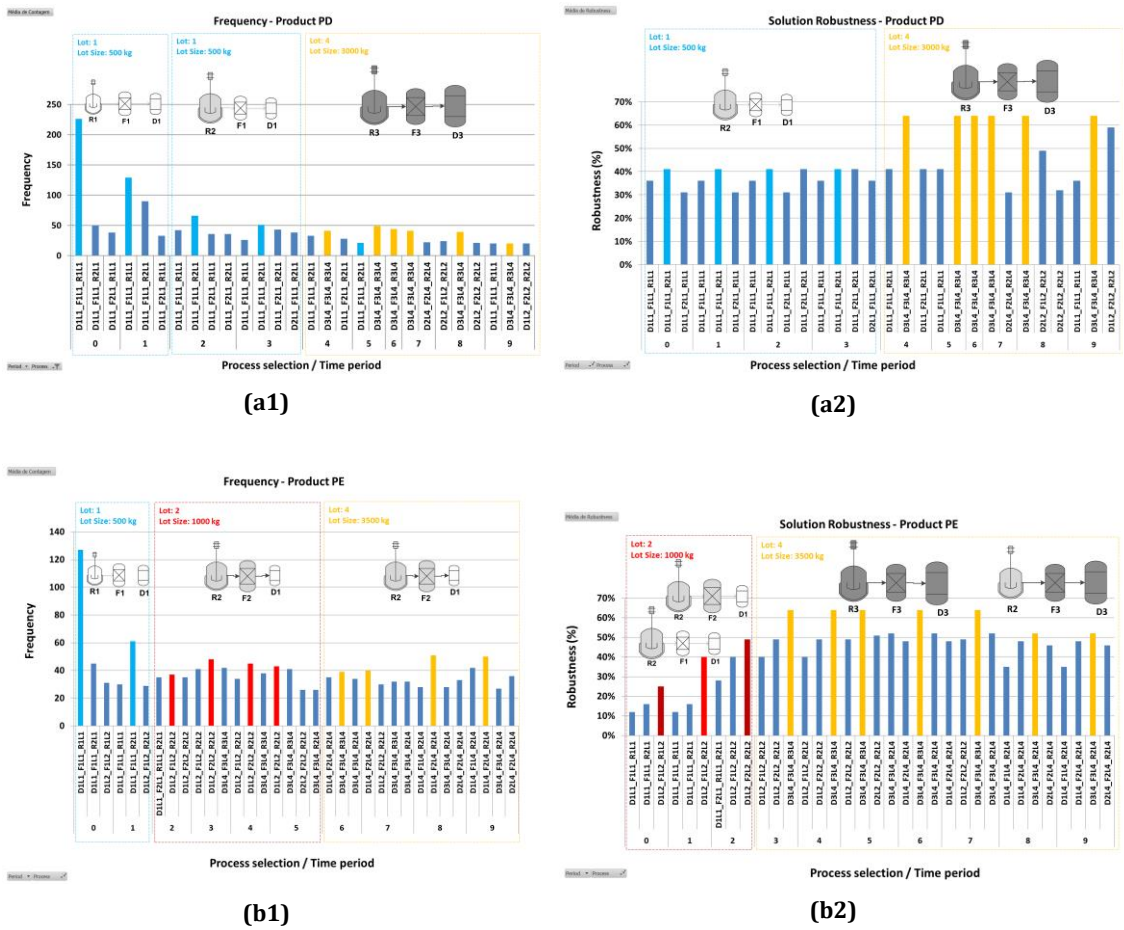


Figure 3.20 Results for the products already in commercialization including uncertainty in processing times: (a) process design selection; (b) solution robustness.

Finally, concerning the capacity extension, there are also some differences. Although the overall observed capacity extensions for both cases are not significant occurring almost exclusively for reactor R1 (Figure 3.21), when introducing uncertainty in processing times this has a significant increase of about 56% on average. The results obtained for the two situations are compared in Figure 3.22 (these are average values for the 1000 iterations).

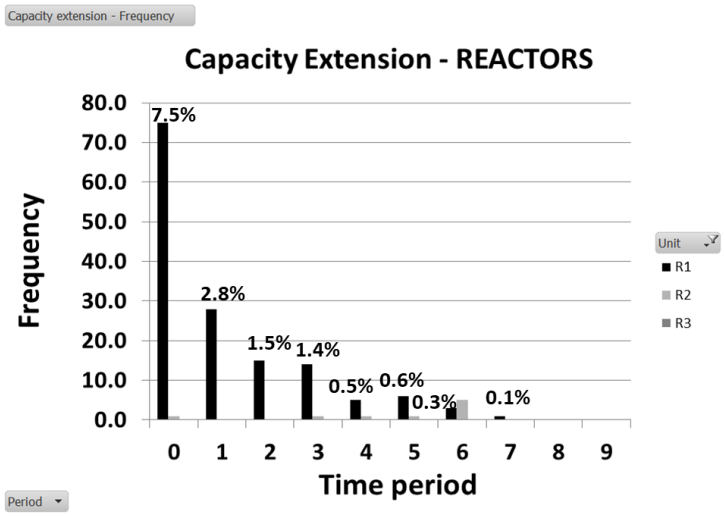


Figure 3.21 Capacity extension frequency for the processing unit type "Reactors" considering uncertainty in processing times.

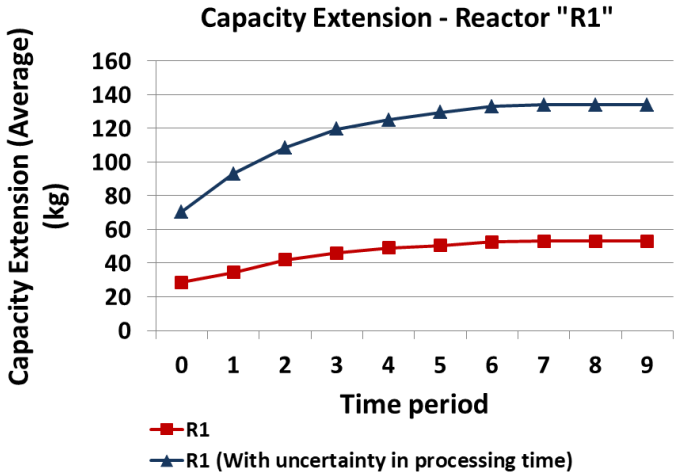


Figure 3.22 Capacity extension for reactor R1, with and without uncertainty in processing time.

These results do therefore provide interesting information on the risks of the decision-making process if not all relevant uncertain parameters are taken into account. It is clear, that uncertainty in processing times is not negligible, even in situations where other types of uncertainty are present. Although, the impact of the processing time variability in the NPV is not significant, the results show that it will inevitably affect the decision-making process, by changing the best strategies in what concerns process design configuration, and times and sizes of scale-ups. This could be explained by the fact that the processing time has a strong influence on the capacity availability since it is expressed in available processing time. In this way, adding uncertainty to the processing times means that will be scenarios in which the processing times are higher than the average values, resulting in

a greater need for production capacity. This may also explain the increase observed in the average computational run time in each iteration.

3.7. Conclusion

This section presents an innovative approach, combining a MILP model and a two-step MCS framework, to address the product-launch planning problem, considering uncertainty on the product demand and on the pass/fail clinical trial tests. The MCS component explores the effects of both types of uncertainty, based on normal and Bernoulli distributions, embedded in a two-step sampling procedure. Later the approach is expanded to also include the uncertainty on processing times, in order to assess its implications on the proposed methodology and its impacts on the overall decision-making process. In this case, the Monte Carlo simulation is performed based on uniform distributions.

The product-launch planning problem is tackled by integrating both process design and planning decisions and considering the resource limitations due to resource sharing among products under development and products already in commercialization. A case study inspired on a real situation from the chemical-pharmaceutical industry was used to demonstrate the applicability of the proposed approach. This approach has proven to be able to efficiently assess the effects of uncertainty in process design and scale-up decisions, as well as in capacity and production planning decisions, during new product development.

The obtained results clearly show the significant influence of the uncertainty parameters on the NPV, on the process design configurations, and on the scale-ups, thus strengthening the idea that deterministic models undoubtedly lead to poor decision-making. Particularly in new drug development, the decisions on process design and on scale-ups are strongly dependent on the uncertainty of pass/fail outcomes of the clinical trials. Since these decisions need to be taken before knowing if the new drugs will succeed in all the clinical trial phases, they are extremely critical in economic terms.

The computational results also show that the proposed method is a robust tool to support this decision-making process, by clearly identifying process configurations and scale-ups that maximize profit, in a highly uncertain context. Moreover, the analysis performed in this study can be useful in the long-term assessment of the process design configurations and their lifetime management. It also provides valuable strategic information for developing solutions that not only maximize the NPV, but also reduce the likelihood of the company to undertake process design changes in the future.

Furthermore, the incorporation of the uncertainty in processing times has demonstrated the ease of adapting the developed approach to additional sources of uncertainty. This is mainly because the MILP model size is independent of the number of uncertainty parameters. In that sense, increasing the number of uncertainties in the problem will not increase the model size or complexity, influencing only the sampling procedure. In that sense, the presented MCS framework proves to be

very flexible, allowing the inclusion of additional steps to the sample procedure to account for several uncertainty parameters simultaneously.

We believe that one of the main benefits of this model is the provision of valuable and robust information in early stages of product development, thus supporting an on-time and better decision-making process. Late decisions will therefore be avoided particularly regarding unnecessary or undersized investments, or possible future changes in the process design configuration. Additionally, this comprehensive analysis of the uncertainty parameters will allow a better coordination between the different decision levels within the company, with a clear gain in what concerns decision flexibility.

Nevertheless, one main limitation of this approach (that is, at the same time, an interesting research challenge) is the inability to establish correlations between different process designs, and consequently to determine the unique *here-and-now* solution. This has motivated the subsequent work presented in the following chapter, in which a new methodology is developed to enhance the proposed decision-making framework and determine the unique strategic (*here-and-now)* solution.

4. Strategic decision-making under uncertainty: a unified framework

This chapter describes the developed multi-objective integer programming model embedded in a unified decision-making framework to determine the final strategic decisions, explicitly considering the decision-maker preferences.

The content of this chapter is based on the work published in an international peer reviewed journal as follows:

Journal publication

Marques, C. M., Moniz, S., & de Sousa, J. P. (2018). Strategic decision-making in the pharmaceutical industry: A unified decision-making framework. Computers & Chemical Engineering, 119, 171-189.

Abstract

The implementation of efficient strategic decisions such as process design and capacity investment under uncertainty, during the product development process, is critical for the pharmaceutical industry. However, to tackle these problems the widely used multi-stage/scenario-based optimization formulations are still ineffective, especially for the first-stage (*here-and-now*) solutions where uncertainty has not yet been revealed.

This study extends the work presented in the previous chapter addressing the stochastic product-launch planning problem, by developing a new Multi-Objective Integer Programming model, embedded in a unified decision-making framework, to obtain the final design strategy that "maximizes" productivity while considering the decision-maker preferences.

An approximation of the efficient Pareto-front is determined, and a subsequent Pareto solution analysis is made to guide the decision process. The developed approach clearly identifies the process designs and production capacities that "maximize" productivity as well as the most promising solutions region for investment. Moreover, a good balance between investment and capacity allocation was achieved.

4.1. Introduction

4.1.1. Motivation

In the pharmaceutical industry the ability to bring new drugs into the market consistently is a central issue to remain competitive and maintain economic sustainability. The new product development (NPD) process is therefore a critical step towards this objective. Several challenges arise during this phase, and companies are typically faced with a twofold problem: (i) ensure a sound portfolio management in the development pipeline (Laínez et al., 2009a), and (ii) guarantee efficient process design and planning decisions during the clinical trials, in order to enhance R&D productivity and deliver medical drugs faster and more efficiently (Paul et al., 2010b). However, in the past years not only a decreasing number of approved new medicines have been experienced by the industry, but also the cost per approved new compound has been increasing (DiMasi et al., 2016), being the clinical trials the most expensive activity of the development process (EFPIA, 2016) (see Figure 2.4). As mentioned previously (chapter 2), more complex and larger clinical trials due to stringent regulations, as well as an increasing focus on the development of more complex molecular entities to address more challenging diseases, are pointed out by some authors as being the basis for this turnaround in the pharmaceutical business context (Pammolli et al., 2011a; DiMasi et al., 2016). In addition to this, the revenue losses due to a reduced market exclusivity and a growing generic competition also contribute to a generalized decrease in the R&D productivity (Grabowski & Vernon,

2000; Shah, 2004; Paul et al., 2010b; Pammolli et al., 2011a). According to Paul et al. (2010b), a dramatic increase in the R&D productivity will be needed in order to compensate the revenue losses due to patent expirations.

Typically, the productivity is measured as the ratio of R&D outputs to inputs or, as stated by Paul et al. (2010b), can be defined as the relation between the "value created" by a new drug and the investment required to generate that new drug. Therefore, companies should focus on enhanced decision-making approaches that takes into consideration the trade-offs between these conflicting goals (Moniz et al., 2015a): increase the "value created" of the R&D activity, while minimizing both, costs and time-to-market. According to Federsel (2010), the focus for companies in this industry should be cost, speed (time-to-market) and decision-making. The implementation of efficient process design and planning decisions will definitely contribute to all of these goals. Therefore, improving the R&D productivity relies greatly in balancing specific strategic decisions during the development phase, such as: what should be the best long-term production process configuration and how much capacity should be allocated/reserved or invested for what products, while accounting the risks mainly associated to clinical trial failures.

The complexity involved in these decisions is significantly amplified by the highly stochastic nature of the development process. Not only the technical uncertainty associated to the clinical trials pass/fail outcome, but also the market uncertainty due to the long development cycles have a significant impact in the decision process and cannot be neglected in these long-term planning decisions. Nevertheless, dealing with uncertainty leads to large-scale and very complex optimization problems hard to solve particularly when involving integer decision variables and multi-period formulations (Sahinidis, 2004; Moniz et al., 2013b). In that sense, predicting the best process design and/or the capacity needs for the uncertain future is still an unsolved problem and a challenge being pursued not only by the academic community, but also industrial practitioners.

In the previous chapter a Monte Carlo simulation-based approach was presented in order to address this challenge. The developed approach gives insight of what might happen in the uncertain future regarding product demand and clinical trials outcomes, and it provides a robust sensitivity analysis for a wide range of scenarios by mapping the alternative decisions with greater probabilities of occurrence. In this manner decision-makers will have at their disposal a valuable set of structured information to support a better decision-making at the early stages of product development.

Nevertheless, despite this methodology has proven to be effective in determining the impacts of several sources of uncertainty in the long-term decision-making process (Marques et al., 2017a; Marques et al., 2017b), the determination of a unique strict solution is not straightforward. Moreover, in this highly stochastic environment the involvement of the decision-maker in finding the "best" decision cannot be disregarded and his preferences as well as risk attitude should be reflected in the final solution.

Thus, there are two fundamental research questions that now prevail:

(i) *How to systematically determine the strategic process design solution based on the results of the simulation framework?*

(ii) *How to "maximize" the productivity in a highly uncertain context while reflecting the decision-maker risk attitude?*

4.1.2. Background

Uncertainty is present in almost every practical problem, although its relevance is particularly significant in planning problems where both technical and market uncertainties arise. As technical uncertainties, clinical trials outcomes, processing times, and production yields are among the most common. Despite the importance of all these uncertainty contributions, the clinical trial outcomes clear stands out as the most significant source of uncertainty (Colvin & Maravelias, 2008), not only because of its challenging discrete, binary nature ("success" or "failure"), but also due to its major economic impact in the product development process. On the other hand, as market uncertainties, product demand, raw material availability and prices are among the most relevant, since they occur during the long drug development cycles.

Explicitly modeling uncertainty leads to great improvement of the solution robustness (Verderame et al., 2010), and the relevance of including it in Process System Engineering (PSE) applications is highlighted by several interesting surveys that have emerged in recent years. Sahinidis (2004), present a review of the main approaches that have been developed to address optimization problems under uncertainty, and identifies three major groups: stochastic programming (including: recourse models, robust stochastic programming, and probabilistic models), fuzzy programming and stochastic dynamic programming. Later, Li & Ierapetritou (2008) focused on production scheduling under uncertainty, presenting a review of the main methodologies developed to address this problem. The authors highlight the vital importance of develop a unified framework for planning and scheduling under uncertainty and to systematically consider all uncertain parameters.

Also, Verderame et al. (2010) focused on planning and scheduling under uncertainty with a review across multiple sectors. Particularly for the chemical, petrochemical and pharmaceutical sector, the authors point out the Two-stage stochastic programming, chance constraint programming, robust optimization, and Value-at-Risk and Conditional Value-at-Risk as the most developed approaches. More recently, Grossmann et al. (2016a) present recent advances in mathematic programming techniques to address optimization under uncertainty in process systems. Stochastic programming, robust optimization, and chance constrain programming are also pointed as being the most relevant approaches to address uncertainty. As stated by the authors Grossmann et al. (2016a) one of the major concerns when modeling under uncertainty rely on the selection of the best optimization approach. The paradigms embedded in each one of these methodologies can give clues regarding the best strategy to follow, yet an efficient approach to tackle uncertainty is still far from being a reality.

While robust optimization is pointed as more suitable for scheduling purposes due to its more conservative orientation, two-stage stochastic programming has been most widely used in more strategic settings in which decisions can be broken into two or more stages (Grossmann et al., 2016a).

Due to the highly strategic nature of the decisions typically involved in the management problems of the NPD process in the pharmaceutical industry, the Two-Stage Stochastic Programming (TSSP) has been one of the most common approaches used to tackle uncertainty. Particularly, when considering uncertainty in the clinical trials outcomes, works can be found covering areas such as, supply chain and capacity planning (Rotstein et al., 1999; Cheng et al., 2003; Gatica et al., 2003b; Gatica et al., 2003a; Levis & Papageorgiou, 2004; Sundaramoorthy et al., 2012), and portfolio management and task scheduling (Schmidt & Grossmann, 1996b; Maravelias & Grossmann, 2001; Levis & Papageorgiou, 2004; Colvin & Maravelias, 2008; Colvin & Maravelias, 2011; Perez-Escobedo et al., 2012; Christian & Cremaschi, 2015).

The two-stage stochastic programming approach gains relevance with the seminal work of Dantzig (1955) in which the essential idea is that decisions are taken in two or more (for multi-stage applications) stages. The first-stage ("here-and-now") decisions are made under significant uncertainty and the second-stage ("wait-and-see") decisions are explicitly determined after the realization of the random events (Dantzig, 1955; Birge & Louveaux, 2011). Since the first-stage decisions do not depend on the outcomes of the uncertain parameters, these are typically associated with strategic decisions, such as network design, plant and process design, investment strategy, portfolio selection, etc. In the second-stage operational decisions such as detailed production plans, and resource allocation will take place. These decisions are quantitatively dependent on the random values and so, to a certain extent, will "correct" the first-stage decisions (Dantzig, 1955; Birge & Louveaux, 2011). According to Malik & Hughes (1979), the design of chemical processes is typically a two-stage problem with a design stage (first-stage) and an operational stage (second-stage) in which the design variables are fixed. However, the numerical complexity and computational burden associated with a monolithic stochastic "here-and-now" program limit their full application and decomposition schemes are usually inevitable to solve the problems.

Moreover, the traditional neutral attitude toward risk of the classical formulation of the TSSP (Dantzig, 1955; Birge & Louveaux, 2011) also limits its application in more embracing problems, in which the decision-maker interaction is encouraged. Especially for the first-stage decisions where uncertainty has not yet been revealed, the decision-maker risk attitude is of great relevance. Despite several studies have been published considering the risk-averse attitude by changing the objective function through the incorporation of some risk measures (Applequist et al., 2000; Shapiro, 2012; Homem-de-Mello & Pagnoncelli, 2016), the effective incorporation of these measures is still a main challenge in TSSP approaches as stated by Grossmann et al. (2016a). In that sense, the current paradigms to tackle uncertainty that lead us to a unique optimal decision without considering the decision maker preferences tends to be inadequate in more practical and realistic settings.

On the other hand, considering that simulation approaches are particularly suited to assess risk under uncertainty contexts, simulation-optimization based approaches seem to be a promising tool to undertake these challenges. Important contributions have been made using simulation-optimization based approaches specifically addressing clinical trials outcomes uncertainty, mainly for portfolio selection and task scheduling (Subramanian et al., 2001; Subramanian et al., 2003; Blau et al., 2004b; Rajapakse et al., 2005; Varma et al., 2008b; Chen et al., 2012a; Perez-Escobedo et al., 2012). Also, Monte Carlo Simulation based approaches have been proposed in the literature addressing different planning problems under uncertainty in the chemical-pharmaceutical industry (Bassett et al. (1997), Farid et al. (2005), Eberle et al. (2014)). All these approaches contribute to a more realistic representation of uncertainty while benefiting from the optimization advantages, however the determination of the final process design solution reflecting the decision-maker preferences have not yet been extensively explored.

An extension of the previous work is presented here to address the stochastic product launch planning problem with an emphasis on the determination of the strategic solutions regarding process designs (including the respective processing units and lot sizes), and capacity planning, taking in consideration the decision-maker preferences and attitude towards risk. Therefore, a solution approach is presented to rigorously determine the unique (*here-and-now*) stochastic solution (based on the results of the previously developed Two-Step Monte Carlo simulation framework) by developing a Multi-Objective Integer Programming (MOIP) model embedded in a unified decision-making framework, with the overall goal of improving the R&D productivity. A compromise solution will be then obtained by balancing the conflicting objectives of increasing the "value created" by the product development process, while minimizing the associated development costs.

4.2. Problem description

The problem considered here is based on the product launch planning problem under uncertainty addressed in the previous chapter in which a detailed description is provided. Nevertheless, for the sake of a better understanding of the present study, the most relevant features of the addressed problem will be briefly described here.

In the previous work a multipurpose batch plant producing simultaneously products under development and products already in commercialization (competing for the same limited resources) was considered. A discrete-time formulation was proposed encompassing several years to accommodate the three clinical trials phases, and ending with the regulatory approval of both, products and production processes. Uncertainty in product demand (for both types of products) and in the clinical trials outcomes (for the products under development) were explicitly considered and captured through the developed Two-Step Monte Carlo Simulation (TSMCS) procedure. The main purpose was then to determine simultaneously process design and planning decisions for a known set of products reaching clinical trial phase I. The key decisions considered were: the best set of

processing units to each process (process design configuration), size and timings of scale-ups (including lot traceability), amounts to produce and store of each product and period, and the capacity extension requirements, in order to maximize the Net Present Value (NPV).

Taking this as basis, in this work the same multipurpose batch plant sharing their resources between the two modes of production is considered as well as the same planning horizon. Although, in this case instead of determining the best production plan over the planning horizon, the goal is to select the "best" strategy to follow in order to guarantee the long-term capacity availability needed to fulfil both types of demand: the clinical trials demand, and the regular products demand, in face of significant uncertainty.

Therefore, a pre-determined set of different process designs is given for each product and period to be selected by the developed optimization model. A "process design" as considered in this work emerges directly from the results obtained in the TSMCS framework previously developed, through the determination of the process/unit assignment binary variables and lot-size integer variables for each product and period. Hence, each "process design" aggregates all individual tasks to produce a specific product, and can be defined by two types of entities, namely: (i) the set of processing units used to perform each individual task (Reactors (R), Filters (F), and Dryers (D)), and (ii) the lot size (L1, L2, L3, and L4), that will guarantee production traceability and production bounds for each product. In that sense, instead of having a typical production recipe (Figure 4.1) to model and determine the best production plan (including capacity and scale-up decisions), a simplified version of the concept of campaign (Moniz et al., 2014a) is used here in which the complete recipe is embedded (Figure 4.2). Thus, each "process design" act like a specific "campaign" characterized by several parameters calculated from the results obtained in the previous simulation model for each period, such as: the cycle time, the minimum and maximum number of cycles, the minimum amount produced per cycle, and the operational and fixed costs.

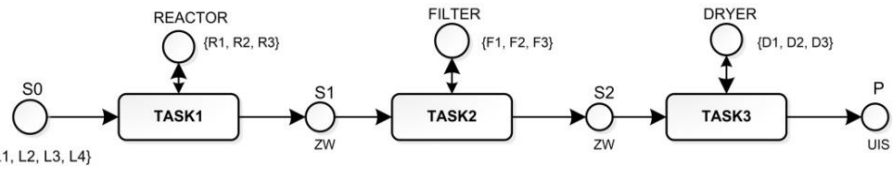


Figure 4.1 Resource-Task-Network process representation to produce a single final product P.

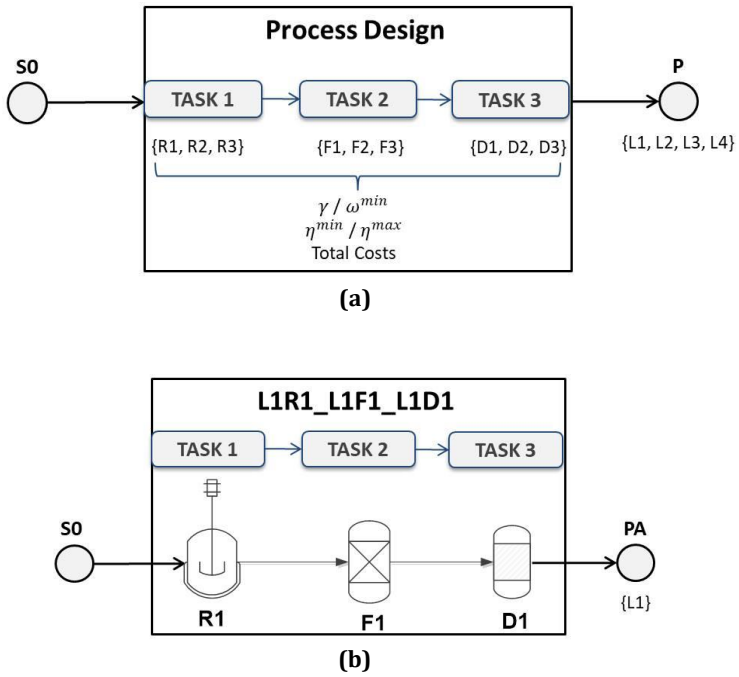


Figure 4.2 Process design detail. (a) Each process design is composed by the production tasks and is defined by the Cycle Time ($\boldsymbol{\gamma}$); minimum amount produced per cycle ($\boldsymbol{\omega^{min}}$); minimum and maximum Number of Cycles ($\boldsymbol{\eta^{min}}/\boldsymbol{\eta^{max}}$) and total costs (fixed and variable); (b) Example of a specific process design, composed by lot size "L1", reactor "R1", filter "F1", and Dryer "D1": L1R1_L1F1_L1D1.

This pre-determined set of process designs correspond to the most frequently selected by the TSMCS framework. Thus, it is assumed that the stochastic nature of the problem has been captured in the simulation framework (TSMCS) and it's reflected in the pre-determined set of process designs considered here (including their respective parameter values). Moreover, the explicitly representation of the production recipes will not be considered in this work, since they are embedded in each process design (Figure 4.2) and the respective detailed production plans were already determined in the previous chapter.

The minimum and maximum numbers of cycles associated to each process design and period as well as the respective cycle times, and minimum amount produced per cycle are considered given as they are obtained from the simulation results. The probabilities of market success for each product under development are also given in order to evaluate the most promising products in the development pipeline.

Therefore, the problem under consideration consists in determining the final strategic solution, selecting for each product and period the "process designs" that "maximize" productivity while simultaneously, considering the decision-makers preferences.

Additionally, process changes over the planning horizon are highly undesirable, due to the high cost, and time-consuming involved, so a penalty cost is introduced to minimize this problem.

Considering the above description, the problem being addressed can be formally defined as follows.

Given:

(i) a fixed time horizon, discretized into several time periods of equal duration ($t \in \mathbf{H}$);

(ii) the set of under development products entering clinical trials ($p \in \mathbf{P}^{\mathrm{U}}$);

(iii) the set of products already in commercialization ($p \in \mathbf{P}^{\mathrm{C}}$);

(iv) the set of candidate process designs for each product and period determined in the simulation model (TSMCS) ($j \in \mathbf{J}_{pt}$);

(v) the lot sizes associated to each process design ($l \in \mathbf{L}_{\mathrm{j}}$);

(vi) the set of processing units initially available in the plant ($e \in \mathbf{E}$);

(vii) the maximum and minimum number of cycles for each process design determined from the simulation (TSMCS) results;

(viii) the cycle times associated to each product, process design, and processing unit determined from the simulation (TSMCS) results;

(ix) the probabilities of market success in each clinical trial phase for each under development product ($p \in \mathbf{P}^{\mathrm{U}}$);

(x) all operational, fixed, and penalty costs associated to each process design, as well as the sales prices of each product;

Determine:

(i) the "process design" allocation for each product and time period (X_{pjlt});

(ii) the number of cycles associated to each process design (NC_{pjlt});

In order to:

(i) "maximize" productivity through a proper balance between production costs and production capacity, and reflecting the decision-maker preferences.

Figure 4.3 depicts a schematic representation of the problem being addressed and the main decisions involved, such as: process design allocation (X_{pjlt}), and the respective number of cycles (NC_{pjlt}).

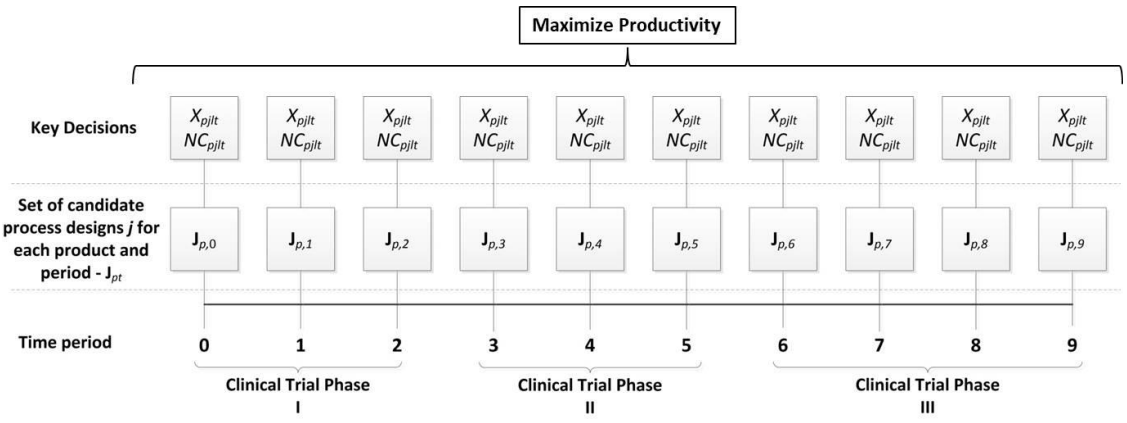


Figure 4.3 Schematic representation of the problem under study. The set of candidate process designs J_{pt} for each product and period and the respective key decisions ($\boldsymbol{X_{pjlt}}$ binary variables and $\boldsymbol{NC_{pjlt}}$ integer variables) are presented.

4.3. Conceptual decision-making framework

The proposed solution is an extension of the previously developed Two-Step Monte Carlo Simulation (TSMCS) framework in order to complete the decision-making process by determining the final design strategy of the stochastic product launch planning problem.

Following the two-stage stochastic programming paradigm (Dantzig, 1955; Malik & Hughes, 1979; Birge & Louveaux, 2011), decisions under uncertainty may be taken in two main stages: the "here-and-now" and the "wait-and-see" decisions. The focus of the proposed approach is therefore to find the unique strategic solution (i.e. the "here-and-now" solution in the TSSP paradigm) that was not directly achieved by the proposed TSMCS framework.

According to Malik & Hughes (1979), to tackle the "here-and-now" problem three simpler problems usually arise: the Most Likely (deterministic) problem (ML) in which expected values are used for all uncertain parameters, the Expectation problem (EX) in which the most likely (deterministic) design is fixed and evaluated by computing the expected value over the probabilistic distributions of the uncertain parameters, and the Wait-and-See problem (WS) in which the expected value is determined over the probabilistic distributions of the uncertain parameters with respect to all variables (both design and operational variables). According to the authors, by assessing these three problems individually, some conclusions are possible to be taken regarding the final "here-and-now" solution. However, the underlying idea is based on the current strategies of finding a unique optimized solution without any involvement of the decision-maker. Therefore, based on the main paradigms embedded in the above concepts, and their existing gaps, a new unified conceptual framework is developed to tackle the "Here-and-Now" problem in which several sources of uncertainty can be considered simultaneously, and the decision-maker preferences are taken into account to guide the final solution.

The proposed unified decision-making framework links the simulation procedure developed in chapter 3 with the Multi-Objective Integer Programming (MOIP) model developed in this study. In the first part of the framework (simulation procedure) the set of candidate process designs are determined under considerable uncertainty, and in the second part of the framework, the final solution is determined. The complete framework is depicted in Figure 4.4, including 5 main steps: 1. "Solutions generation"; 2. "Set of candidate solutions"; 3. "Pareto frontier"; 4. "Performance assessment", and 5. Strategic final solution". The main idea of this framework is to use the MOIP model to select the final solution from the most frequently selected process designs obtained in the previous simulation procedure.

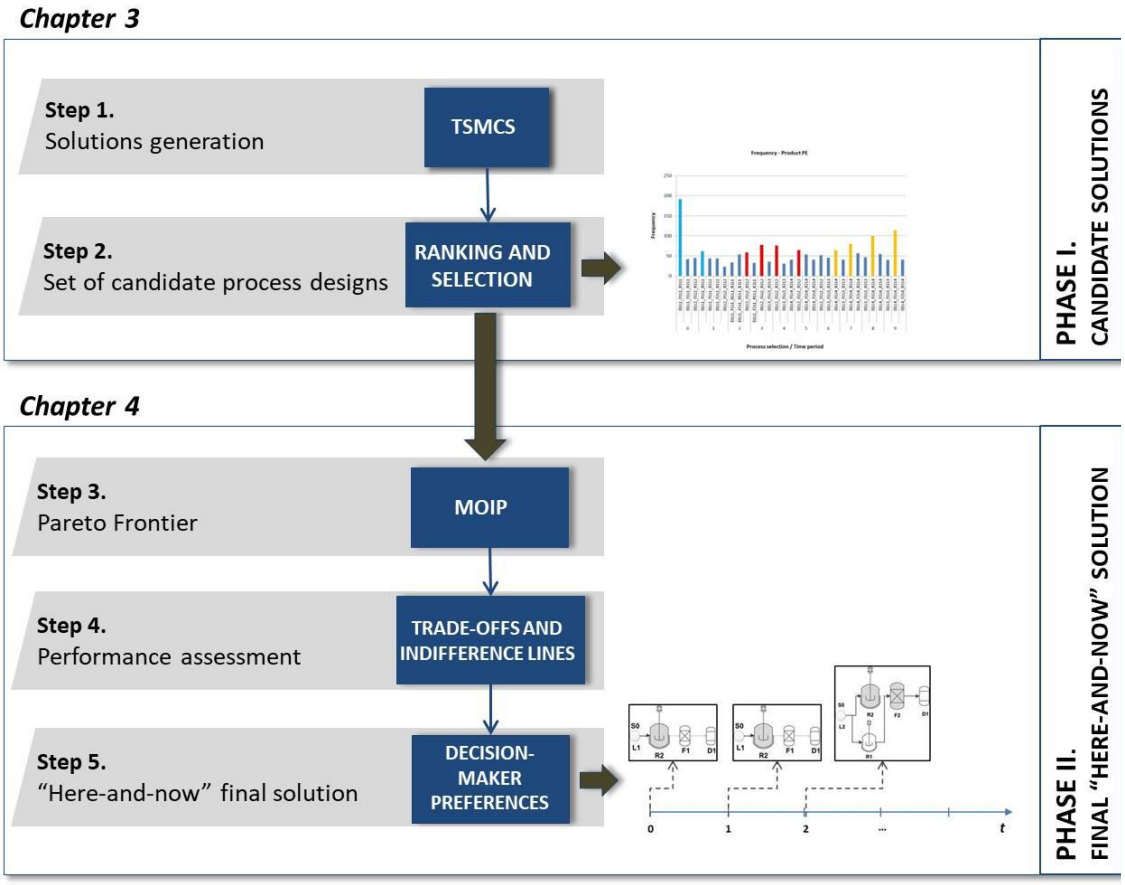


Figure 4.4 Unified decision-making framework, integrating the TSMCS framework with the MOIP model.

The first part of the framework is divided in two steps (Step 1 and step 2). In the first step, solutions are generated through the TSMCS procedure in which the simultaneous impact of uncertainty in product demand and in clinical trials outcomes are assessed. In each iteration of the Monte Carlo sampling process a deterministic solution is obtained for a specific realization of the uncertain parameters with respect to all decision variables (both strategic and operational).

A probabilistic distribution for the objective function and histograms for each decision variables are obtained and analysed. A parallelism may be found between this step and the Wait-and-See problem described in the work of Malik & Hughes (1979), but instead of computing the mean value to obtain a final solution, here the entire range of values is analysed by probabilistic distributions and frequency of occurrences, contributing to a more reliable and robust final solution. In the second step, the solutions found previously are ranked according to the most frequent solutions obtained for the process design configurations (the strategic design variables). The most frequent process designs for each product and period will integrate the set of candidate final solutions. These first two steps are described in detail in chapter 3 (see section 3.4 and 3.5).

The second part of the proposed framework is performed in three steps (Step 3, 4, and 5) and is focused on the determination of the final decision. Starting with step 3, a Multi-Objective Integer Programming (MOIP) model is developed to select, for each product and period, the unique process design solution (from the candidate process designs obtained in step 2). The weighted-sum method

is used to determine a specific solution by assigning weights to each objective function, reflecting their relative importance (a detailed description of the MOIP model is presented in section 4.4). An approximation of the Pareto efficient frontier is then constructed by generating multiple sequential solutions through a consistent variation of the weight's combination. A Pareto analysis is then performed by the decision-maker in order to select a unique solution. Nevertheless, the selection of the unique solution among all the others may be a challenging process and so a subsequent Pareto analysis with a performance assessment of the solutions is introduced in the framework (step 4) to help the decision-maker evaluate the available solutions and identify the preferred one. Therefore, in step 4, a performance assessment is made by determining different trade-off values and the respective indifferent lines to be analysed by the decision-maker (Keeney & Raiffa, 1993). Each trade-off value corresponds to a productivity level associated to a specific solution in the Pareto frontier. Finally, in the last step of this framework (Step 5) the final solution (i.e. process design configuration) is determined based on the risk attitude of the decision-maker and his preferences. These three last steps (Steps 3, 4 and 5) correspond to the main contributions of this chapter and will be described in detail in the following sections.

4.4. Multi-Objective Integer Programming (MOIP) model

A Multi-Objective Integer Programming (MOIP) model is developed to select the process design configurations for each product and period, over a planning horizon of several years in order to "maximize" productivity. The key decision variables are the *process design/product assignment* binary variables (X_{pjlt}), and the *number of cycles* integer variables (NC_{pjlt}). The detailed mathematical formulation of the model is presented in the next sections with the description of the constraints and objective functions.

NOTATION

Indices

j	Process design
l	Lot
p	Final product
t	Period
e	Processing units
k	Objective functions

Sets

H	Planning horizon
J	Sub-set of candidate process designs
$\mathbf{J}_p$	Process designs associated with product $p \in \mathbf{P}$
$\mathbf{J}_{pt}$	Process designs associated with product $p \in \mathbf{P}$ and period $t \in \mathbf{H}$
$\mathbf{J}_{et}$	Process designs associated with processing unit $e \in \mathbf{E}$ and period $t \in \mathbf{H}$
L	Lots
$\mathbf{L}_j$	Lots associated with process $j \in \mathbf{J}$
P	Final products

E	Processing units
E_j	Processing units associated with process design *j*

Parameters

γ_{pjlet}	Cycle time associated to each product *p* process design *j* lot *l* processing unit *e* and period *t* (h)
α_{pjl}^{var}	Variable component of the operational cost of each process design *j* for product *p* and period *t* (rmu)
α_{pjl}^{fix}	Fixed component of the operational cost of each process design *j* for product *p* and period *t* (rmu)
α_{pt}^{pc}	Penalty cost for process changes that occurs in each product *p* and period *t* (rmu)
τ_e	Available capacity for each processing unit *e* expressed in time availability (h)
τ^{chg}	Changeover time (h)
$\eta_{pjlt}^{max}/\eta_{pjlt}^{min}$	Maximum and minimum number of cycles associated to each product *p* process design *j* lot *l* and period *t*
ω_{pjt}^{min}	Minimum amount that can be produced in one cycle of the process design *j* associated to product *p* and period *t* (kg)
ρ_{pt}	Probability of each product *p* to reach the market at each period *t*
ϑ_{pt}	Value of each product *p* at each period *t* (rmu)
β_k	Weighting factor for the multi-objective function *k*
f_k^{UB}/f_k^{LB}	Upper and lower bound of objective function *k*

Binary variables

X_{pjlt}	Equal to 1 if process design *j* and lot *l* are selected for product *p* at period *t*
C_{pt}	Equal to 1 if process design of product *p* changes in period *t* (auxiliary variables)

Integer variables

NC_{pjlt}	Number of cycles for product *p* of process *j* with lot size *l* in period *t*

4.4.1. Constraints

Assignment constraints

$$\sum_{j\in\mathbf{J}_{pt}}\sum_{l\in\mathbf{L}_j} X_{pjlt} = 1 \quad \forall p \in \mathbf{P}, t \in \mathbf{H} \tag{4.1}$$

Equation (4.1) concerns the assignment constraints and is used to select a process design *j* with a lot-size *l* for each product *p* and period *t* through the binary variables X_{pjlt} (equal to 1 if a process is selected). These constraints guarantee that exactly one process design will be selected for each product and period.

Lot constraints

$$X_{pjlt} + X_{pj'l't'} \leq 1 \quad \forall p \in \mathbf{P}, j, j' \in \mathbf{J}_{pt}: j \neq j', l, l' \in \mathbf{L}: l' > l, t \in \mathbf{H}, t' \in \{0, \dots, t\} \tag{4.2}$$

Constraints (4.2) are used to model the scale-up decisions by ensuring that the size of the lots never decreases over the planning horizon.

Process Changes constraints

$$C_{\boldsymbol{pt}} \geq X_{pjlt} + X_{pj'l't-1} - 1 \qquad \forall p \in \mathbf{P}, j, j' \in \mathbf{J}_{pt} : j \neq j', l \in \mathbf{L}_j, l' \in \mathbf{L}_{j'}, t \in \mathbf{H} : \mathrm{t} > 0 \tag{4.3}$$

Constraints (4.3) are used to model the process changes that may occur during the planning horizon. The binary variables $C_{\boldsymbol{pt}}$ represent the process changes of product *p* in period *t*, being equal to 1 if a process change occurs between *t*-1 and *t*, and 0 otherwise.

Number of cycles constraints

$$\eta_{pjlt}^{min} X_{pjlt} \leq NC_{pjlt} \leq \eta_{pjlt}^{max} X_{pjlt} \qquad \forall\, p \in \mathbf{P}, j \in \mathbf{J}_p, l \in \mathbf{L}_j, e \in \mathbf{E}_j, t \in \mathbf{H} \tag{4.4}$$

Constraints (4.4) ensure that the integer variables number of cycles (NC_{pjlt}) are bounded by the minimum and maximum values ($\eta_{pjlt}^{min}/\eta_{pjlt}^{max}$) determined based on the results of the TSMCS procedure. The maximum value is estimated in order to accommodate the higher production amounts found in the simulation results for each product *p*, process design *j* with lot-size *l*, and period *t*.

Capacity constraints

$$\sum_{p\in\mathbf{P}} \sum_{j\in\mathbf{J}_{et}} \sum_{l\in\mathbf{L}_j} \left(NC_{pjlt}\gamma_{pjlet}\right) + \sum_{p\in\mathbf{P}} \sum_{j\in\boldsymbol{J_{et}}} \sum_{\boldsymbol{l}\in\boldsymbol{L_j}} \left(X_{pjlt}\tau^{chg}\right) - \tau^{chg} \leq \tau_{\boldsymbol{e}} \qquad \forall\, e \in \mathbf{E}, t \in \mathbf{H} \tag{4.5}$$

Equation (4.5) denotes the production capacity constraints expressed by the time availability of processing unit *e* in each time period *t*. The first summation represents the total time required to execute the process design *j* in equipment *e*. The parameter γ_{pjlet} is given and represents the cycle time associated to a specific product *p,* process design *j*, equipment *e,* at period *t*. This value was obtained considering the minimum number of batches obtained in the simulation results, thus representing the minimum processing time associated to the processing units *e* and lot *l* of each process design. The integer variables NC_{pjlt} represent the total number of cycles to be executed for the selected process design in period *t.* The second summation defines the changeover times associated to each equipment *e*. Since this formulation is an aggregate model, detailed task-sequencing constraints are not considered, and so exact changeover times cannot be captured. Nevertheless, the minimum amount of changeovers is considered here to make the final solution more reliable. In that sense, the third term (τ^{chg}) is added to the formulation in order to eliminate overestimation of changeovers in the cases in which the last product to be produced in period $\boldsymbol{t}$ is the same to be produced at the beginning of the following period ($\boldsymbol{t}$ + 1). This term ensures that the number of changeovers is equal to the number of products minus one (Erdirik-Dogan & Grossmann, 2007; Moniz et al., 2014a). The parameter τ^{chg} denotes the changeover times and is considered given.

Variables domain

$$\begin{aligned} X_{pjlt} &\in \{0,1\} && \forall\, p \in \mathbf{P}, j \in \mathbf{J}, l \in \mathbf{L}, t \in \mathbf{H} \\ C_{\boldsymbol{pt}} &\in \{0,1\} && \forall\, p \in \mathbf{P}, t \in \mathbf{H} \\ NC_{pjlt} &\in \mathbb{Z}_{+} && \forall\ p \in \mathbf{P}, j \in \mathbf{J}, l \in \mathbf{L}, t \in \mathbf{H} \end{aligned} \tag{4.6}$$

Finally, equations (4.6) define the variables domain.

4.4.2. Objectives

4.4.2.1. Productivity level

The main objective of the problem in study is the maximization of the productivity during the new drug development process considering the limited resources for the simultaneous production of products under development and products already in commercialization.

The general definition of productivity is typically presented as the relation between the outputs and inputs of a process. Based on this, and on the concepts presented by Paul et al. (2010b) in which R&D productivity is defined as the relation between the value created by a new drug and the investment required to generate that drug, the productivity level as considered in this work is expressed by equation (4.7) for each product p.

$$\text{Productivity Level}(p) = \frac{Value\ Created(p)}{Total\ Cost(p)} = \frac{\rho_p \times V_p}{TC_p} \qquad \forall p \in \mathbf{P} \tag{4.7}$$

Here, ρ_p represents the technical success of product p, which is the probability of that product successfully pass all clinical trial phases and reach the market. The V_p corresponds to the product commercial value, and TC_p denotes the total cost invested (including design and operational costs) to develop the product *p.*

In this work, the productivity concept has been adapted to consider not only the products in the development pipeline (as defined by Paul et al. (2010b)), but also the products already in commercialization to capture the effort that is made by the pharmaceutical companies in accommodating in the same plant the simultaneous production of these two types of products during the development phase. Thus, the value created is expressed in potential value for the products under development (since it depends on the probability of technical success) and in the "real" value for the products in commercialization (for which the ρ_p value equals 1).

Therefore, the general equation for the pharmaceutical productivity during the NPD process results from the summation of the productivity levels associated to each product over the entire planning horizon, as defined in Eq. (4.8).

$$\text{Productivity Level} = \frac{\sum_{p\in\mathbf{P}}\sum_{t\in\mathbf{H}}\left(\rho_{pt}\times V_{pt}\right)}{\sum_{p\in\mathbf{P}}\sum_{t\in\mathbf{H}}\left(TC_{pt}\right)} \tag{4.8}$$

The difficulty in considering productivity as the main objective to be maximized is the non-linearity nature of equation (4.8). This, however, falls into a special case of nonlinear programming (NLP) known as linear fractional program (LFP) in which the objective function is the ratio between two linear functions subject to a set of linear constraints. Several methods can be used to solve LFP problems, including the Dinkelbach's algorithm as proposed in (You et al., 2009). Nevertheless, in this work the productivity equation is broken in two terms and a multi-objective optimization model is developed allowing the decision-maker to express his preferences in the choice of the final solution. Thus, two objective functions are now considered: one for the numerator (maximization of value created) and another one for the denominator (minimization of total cost) of equation (4.8) as described below.

4.4.2.2. Total cost (f_1)

The first objective function (Eq. (4.9)) is the minimization of Total Cost (TC) associated to the selected process designs.

$$f_1 \rightarrow \min TC = \sum_{p\in\mathbf{P}}\sum_{j\in\mathbf{J}}\sum_{l\in\mathbf{L}_j}\sum_{t\in\mathbf{H}}\left(\alpha_{pjl}^{var}NC_{pjlt} + \alpha_{pjl}^{fix}X_{pjlt}\right) + \sum_{p\in\mathbf{P}}\sum_{t\in\mathbf{H}}\left(\alpha_{pt}^{pc}C_{pt}\right) \tag{4.9}$$

In the first term, the cost is composed by a variable (α_{pjl}^{var}) and a fixed (α_{pjl}^{fix}) component. The variable component is dependent on the number of cycles (NC_{pjlt}) to be performed for each process design and it includes the operational costs associated to the execution of each one of the production tasks (i.e. reaction, filtration, and drying), and the respective lot-size costs. The fixed component is associated to the process design allocation (X_{pjlt}) and includes the costs associated to the production activation in each one of the processing units that are part of that process design (i.e. reactor, filter, and dryer).

In the second term a penalty cost is introduced to minimize the process changes over the planning horizon, reflecting the setup cost of changing a process. Since this is a critical issue in the pharmaceutical industry, decisions should be taken considering the minimization of the likelihood of future changes in the production process. The penalty cost (α_{pt}^{pc}) varies with the clinical trial phase, being more penalizing as more advanced in its development the product is, since it is expected greater process stability closer to the end of the development process and the regulatory approval.

The cost parameters (α_{pjl}^{var}, and α_{pjl}^{fix}) are determined based on the results obtained from the TSMCS framework. Particularly for the variable cost (α_{pjl}^{var}), this is determined considering the cost of execution of all tasks associated to a specific process design (see Figure 4.2), considering the minimum number of batches obtained in the simulation results. In this manner a cost per cycle is obtained for

each process design configuration. Regarding the fixed cost (α_{pjl}^{fix}), this is determined based on the processing units allocation costs used in the TSMCS framework.

4.4.2.3. Value created (f_2)

The second objective function (Eq. (4.10)) is the maximization of the "Value created" (V) by the company during the New Product Development process considering the simultaneous production of the products under development to supply the clinical trials and the regular products to fulfill the market demand.

$$f_2 \rightarrow \max V = \sum_{p\in\mathbf{P}} \sum_{j\in\mathbf{J}} \sum_{l\in\mathbf{L}_j} \sum_{t\in\mathbf{H}} \omega_{pjt}^{min} \vartheta_{pt} \rho_{pt} NC_{pjlt} \tag{4.10}$$

The "Value created" as considered in this work is inspired by the concepts of pharmaceutical R&D productivity defined by Paul et al. (2010b), and results from the product of the following parameters: i) amount produced in each cycle for a specific process design and product (ω_{pjt}^{min}); ii) sales value of each final product p and period t (ϑ_{pt}); iii) probability of each product p to reach the market at period t (ρ_{pt}), with the decision variables number of cycles (NC_{pjlt}). For the regular products (already in commercialization), the probability of market success is considered 1. On the other hand, for the products under development the probability of market success varies with the clinical trial phase, being lower at the first phase (when uncertainty is higher) and higher in the last phases of development (when more information about the product is available). These values are determined from the probabilities of clinical trial success used in the TSMCS procedure.

Regarding the minimum amount produced in each cycle by a specific process design (ω_{pjt}^{min}), this is defined by the lot-size of that process design and by the minimum number of lots that occurred in the TSMCS results for that specific process design (same assumption used in the estimation of the variable cost parameter).

4.4.3. Multi-objective approach

Taking in consideration the two objective functions defined above, the decisions involved in this problem need to accommodate several trade-offs arising from the production planning problem with the minimization of the production costs ("Total cost"- Eq. (4.9)), and from the product pipeline management problem with the maximization of the production capacity according to the most valuable (market value) and promising (most likely to reach the market) products ("Value created" - Eq. (4.10)). Since increasing the number of cycles in Eq. (4.9) and (4.10), increases not only the value created but also the total cost, a proper balance between these two conflicting objectives should be achieved. Thus, a multi-objective approach is proposed, and instead of determining the optimal strategic solution, a compromise solution among these two objectives will be obtained, reflecting the decision-maker preferences.

Typically, the majority of multi-objective optimization methods fall into *a priori* or *a posteriori* methods, depending on the moment in which the decision maker preferences are expressed (Marler & Arora, 2004; Mavrotas, 2009). On one hand, in an *a priori* approach the decision maker must have a fully understanding about the importance of each objective which may not be easy, since it is seldom obvious or straightforward in the majority of the real-life problems. On the other hand, in *a posteriori* methods instead of a single global solution, a set of efficient solutions (Pareto optimal set or sub-set) are determined and then the decision-maker selects the most preferred solution among them. According to Pareto (1906), the Pareto optimal solutions are the ones that cannot be improved in one objective function without deteriorating at least one of the other objective functions.

In this work an *a posteriori* based approach will be developed, using the well-known weighted sum method, in order to enable the decision maker to establish their preferences directly on the Pareto optimal solutions.

The weighted sum method is one of the simplest and most widely used methods to solve multi-objective optimization problems. In order to determine a single suitable solution, the decision-maker preferences should be incorporated for the different objectives (Zadeh, 1963; Marler & Arora, 2010).

Mathematically, the general weighted sum method for the multi-objective optimization can be stated as follows:

$$\min F = \sum_{k \in \mathbf{K}} \beta_k \bar{f}_k \tag{4.11}$$

$$0 \leq \beta_k \leq 1 \quad \forall\, k \in \mathbf{K} \tag{4.12}$$

$$\sum_{k \in \mathbf{K}} \beta_k = 1 \tag{4.13}$$

Where, β_k correspond to the weighting factors reflecting the decision-maker preferences for the objective function k, and $\bar{f}_k$, correspond to the normalized objective functions. Several approaches can be found in the literature for the normalization procedure, in this work the adopted methodology is given by Eq. (4.14), as it is considered one of the most robust approaches (Marler & Arora, 2004).

$$\bar{f}_k = \frac{f_k - f_k^{LB}}{f_k^{UB} - f_k^{LB}} \qquad \forall\, k \in \mathbf{K} \tag{4.14}$$

Where the f_k^{LB} and f_k^{UB} correspond to the lower and upper bounds respectively of the objective function k, resulting in all objective functions scaled from zero to one. The upper and lower bounds are obtained by optimizing each objective function individually.

4.5. Results and Discussion

4.5.1. Case description

The same case study described in chapter 3 is used here as a basis to validate the proposed decision-making framework and its most relevant features will be outlined in this section.

The product portfolio is composed by 3 products under development (PA, PB, and PC) entering clinical trials phase I, and 2 regular products (PD and PE) already in commercialization. A planning horizon of 5 years discretized into 10 periods of 6 months is considered. The planning horizon is divided in the three clinical trial phases: 1.5 years for clinical trial phases I and II, and 2 years for the clinical trial phase III. The product demand profiles for each one of the products are the same considered in chapter 3 (Figure 3.5).

The probability of each product to reach the market (successfully pass all clinical trials) and the respective unitary values for each period are given and presented in Table 4.1. The probability values were calculated from the probabilities of technical success in each clinical trial phase (pass/fail) used in the Bernoulli distributions embedded in the TSMCS procedure, and based on the studies of DiMasi (DiMasi et al., 2010; DiMasi et al., 2013; DiMasi et al., 2016). In this work, only specific values are considered (rather than probability distributions), since they are used here as a criterion to identify the most promising (most likely to reach the market) products in which it is worth to invest in capacity.

Table 4.1 Unitary value (ϑ_{pt}) and probability to reach the market (ρ_{pt}) for each product and period

t	Products under development						Products in commercialization			
	PA		PB		PC		PD		PE	
	ϑ_{pt} (rmu)	ρ_{pt}	ϑ_{pt} (rmu)	ρ_{pt}	ϑ_{pt} (rmu)	ρ_{pt}	ϑ_{pt} (rmu)	ρ_{pt}	ϑ_{pt} (rmu)	ρ_{pt}
0	50	0.20	35	0.26	45	0.14	55	1	70	1
1	50	0.20	35	0.26	45	0.14	55	1	70	1
2	50	0.20	35	0.26	45	0.14	55	1	70	1
3	50	0.32	35	0.38	45	0.23	55	1	70	1
4	50	0.32	35	0.38	45	0.23	55	1	70	1
5	50	0.32	35	0.38	45	0.23	55	1	70	1
6	50	0.70	35	0.75	45	0.65	55	1	70	1
7	50	0.70	35	0.75	45	0.65	55	1	70	1
8	50	0.70	35	0.75	45	0.65	55	1	70	1
9	50	0.70	35	0.75	45	0.65	55	1	70	1

The production of each product is made following an aggregated recipe embedded in each process design available to be selected in each period of the planning horizon (the recipe details and the respective production plan can be found in chapter 3). In that sense, the production needs to fulfil each product demand (considering uncertainty in product demand and clinical trials outcomes), were determined by the TSMCS procedure and transposed to the MOIP model through the set of

candidate process designs and their respective parameter values. The minimum amount produced per cycle for each process design and their respective minimum and maximum acceptable number of cycles expresses the production range observed in the simulation which in turn reflects the variability in the uncertainty parameters.

The pre-determined set of candidate solutions is considered given and was obtained by the first two steps of the decision-making framework (Figure 4.4). The first step consists of generating all possible solutions by performing the Two-Step Monte Carlo Simulation (TSMCS) framework. The process designs configurations are then determined by the allocation binary variables of the MILP model integrated in the TSMCS framework, which assign the available processing units to tasks, lot-sizes and products. The processing unit types that are part of the process designs are the ones described in Figure 3.7.

A total of more than 2,000 different process designs were obtained for 1000 iterations of the TSMCS framework. The complete set of solutions is depicted in Figure 4.5(a) for all products and periods.

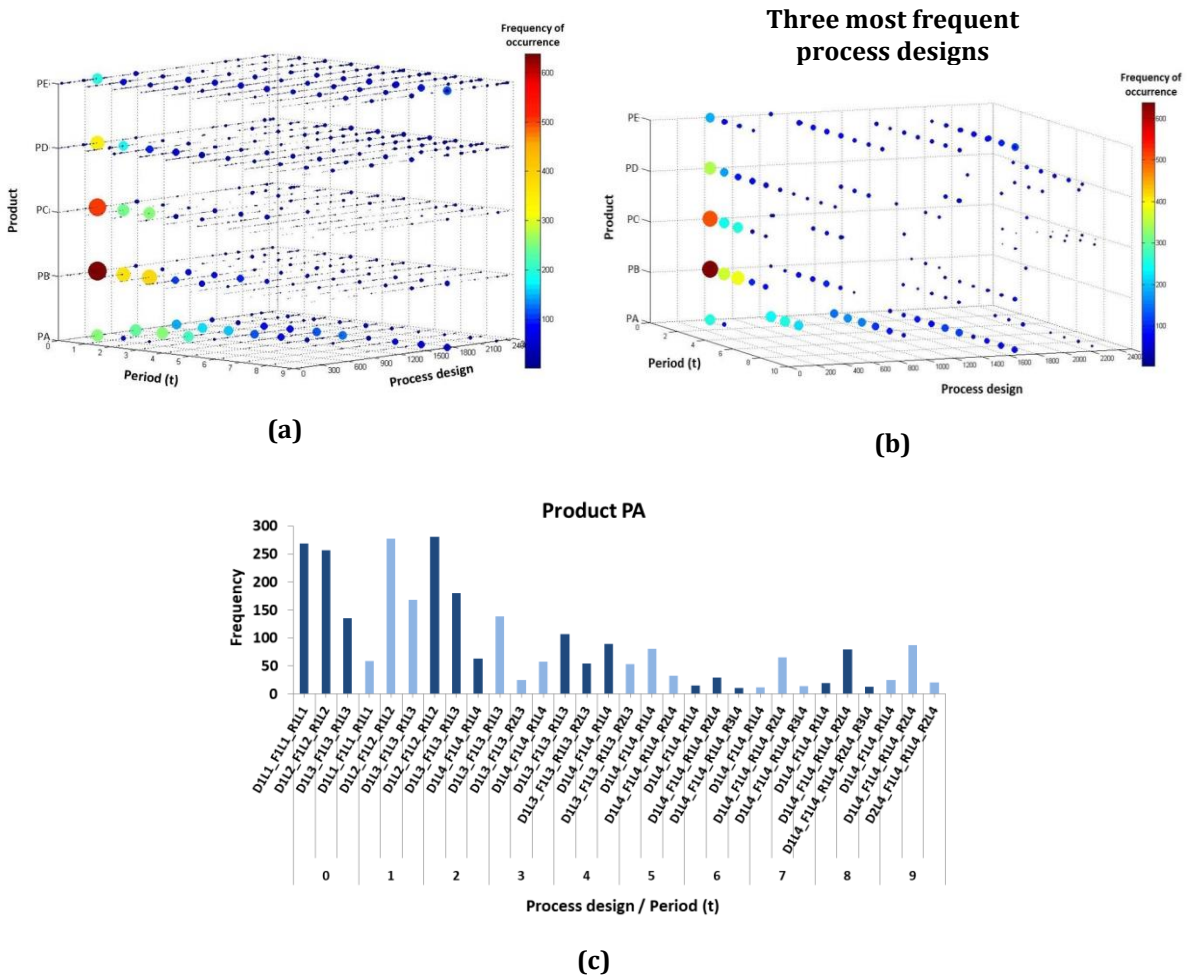


Figure 4.5 Solutions (process designs) obtained for 1000 iterations of the TSMCS framework: (a) complete set of solutions; (b) the sub-set composed by the three most frequent process designs for each product and period, and (c) detail of the three most frequent process designs obtained for product PA in each period *t*.

The size of the bubbles represents the frequency of occurrence of each process design, and for each product and period there is approximately three or four product designs that stand out with a higher frequency value. Since each iteration corresponds to a specific realization of the uncertainty parameters, the most frequent solutions will also correspond to the most probable scenarios of the uncertain future. Therefore, these most frequent process designs for each product and period are selected to integrate the candidate strategic solutions as depicted in Figure 4.5(b). The detailed information regarding the most frequent process designs selected for the product PA is illustrated in Figure 4.5(c) as an example. The complete set of candidate process designs (for all products and periods) is presented in Table 4.2 and the respective parameter data is presented in Appendix D - Table D.1.

Table 4.2 Set of candidate solutions ($\mathbf{J}_{pt}$) for each product and period

t	Products under development			Products in commercialization	
	PA	PB	PC	PD	PE
0	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1
	D1L2_F1L2_R1L2	D1L1_F1L1_R2L1	D1L1_F1L1_R2L1	D3L1_F1L1_R1L1	D1L1_F1L1_R1L1_R2L1
	D1L3_F1L3_R1L3	D1L2_F1L2_R1L2	D1L2_F2L2_R2L2	D1L1_F1L1_R2L1	D1L1_F1L1_R2L1
1	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1
	D1L2_F1L2_R1L2	D1L1_F2L1_R1L1	D1L1_F1L1_R2L1	D1L1_F1L1_R2L1	D1L1_F1L1_R2L1
	D1L3_F1L3_R1L3	D2L1_F1L1_R1L1	D2L1_F1L1_R1L1	D1L1_F2L1_R1L1	D1L1_F2L1_R1L1
2	D1L2_F1L2_R1L2	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L2_F1L2_R2L2
	D1L3_F1L3_R1L3	D1L2_F1L2_R1L2	D1L1_F1L1_R2L1	D1L1_F1L1_R2L1	D1L1_F2L1_R1L1_R2L1
	D1L4_F1L4_R1L4	D1L1_F2L1_R1L1	D2L1_F1L1_R1L1	D1L1_D3L1_F1L1_R2L1	D1L1_F1L1_R1L1_R2L1
3	D1L3_F1L3_R1L3	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L1_F1L1_R2L1	D1L2_F1L2_R2L2
	D1L4_F1L4_R1L4	D1L2_F1L2_R1L2	D1L2_F1L2_R1L2	D1L1_F1L1_R1L1	D1L1_F2L1_R1L1_R2L1
	D1L3_F1L3_R2L3	D1L2_F1L2_R2L2	D1L2_F1L2_R2L2	D1L1_F1L1_R1L1_R2L1	D1L2_F2L2_R2L2
4	D1L3_F1L3_R1L3	D1L1_F1L1_R1L1	D1L1_F1L1_R1L1	D1L1_F1L1_R2L1	D1L2_F1L2_R2L2
	D1L4_F1L4_R1L4	D1L2_F1L2_R1L2	D1L2_F1L2_R2L2	D1L1_F1L1_R1L1	D1L3_F1L3_R2L3
	D1L3_F1L3_R1L3_R2L3	D1L2_F1L2_R2L2	D1L2_F1L2_R1L2	D1L1_F1L1_R1L1_R2L1	D1L2_F2L2_R2L2
5	D1L3_F1L3_R1L3_R2L3	D1L2_F1L2_R1L2	D1L2_F2L2_R2L2	D1L2_F1L2_R2L2	D1L2_F1L2_R2L2
	D1L4_F1L4_R1L4	D1L2_F1L2_R2L2	D1L2_F1L2_R2L2	D1L1_F1L1_R1L1	D1L2_F2L2_R2L2
	D1L4_F1L4_R1L4_R2L4	D1L3_F1L3_R1L3	D2L2_F1L2_R2L2	D1L1_F1L1_R2L1	D1L4_F1L4_R2L4
6	D1L4_F1L4_R1L4_R2L4	D1L3_F1L3_R2L3	D3L4_F3L4_R3L4	D1L2_F1L2_R2L2	D1L2_F1L2_R2L2
	D1L4_F1L4_R1L4	D1L3_F1L3_R1L3	D1L2_F1L2_R2L2	D2L2_F1L2_R2L2	D1L4_F1L4_R2L4
	D1L4_F1L4_R1L4_R3L4	D1L2_F1L2_R1L2	D2L3_F2L3_R3L3	D2L2_F2L2_R2L2	D1L3_F1L3_R2L3
7	D1L4_F1L4_R1L4_R2L4	D1L3_F1L3_R2L3	D1L3_F1L3_R2L3	D1L2_F1L2_R2L2	D1L4_F1L4_R2L4
	D1L4_F1L4_R1L4	D1L3_F1L3_R1L3	D1L2_F2L2_R1L2_R2L2	D2L2_F1L2_R2L2	D1L2_F1L2_R2L2

t	Products under development			Products in commercialization	
	PA	PB	PC	PD	PE
	D1L4_F1L4_R1L4_R3L4	D1L4_F1L4_R1L4	D2L3_F2L3_R3L3	D1L4_F1L4_R2L4	D1L3_F1L3_R2L3
8	D1L4_F1L4_R1L4_R2L4	D1L4_F1L4_R2L4	D2L3_F2L3_R2L3	D1L2_F1L2_R2L2	D1L4_F1L4_R2L4
	D1L4_F1L4_R1L4	D1L3_F1L3_R1L3	D1L3_F2L3_R3L3	D1L3_F1L3_R1L3	D1L2_F1L2_R2L2
	D1L4_F1L4_R1L4_R2L4_R3L4	D1L4_F1L4_R1L4	D2L3_F2L3_R3L3	D1L4_F1L4_R2L4	D1L3_F1L3_R2L3
9	D1L4_F1L4_R1L4	D1L4_F1L4_R2L4	D2L4_F2L4_R3L4	D1L2_F1L2_R1L2	D1L4_F1L4_R2L4
	D1L4_F1L4_R1L4_R2L4	D1L4_F1L4_R1L4	D2L3_F2L3_R2L3	D1L2_F1L2_R2L2	D1L4_F1L4_R1L4
	D2L4_F1L4_R1L4_R2L4	D1L3_F1L3_R1L3	D1L3_F2L3_R3L3	D1L3_F1L3_R1L3	D1L3_F1L3_R2L3

4.5.2. Computational results

The MOIP model was implemented using IBM ILOG CPLEX Optimization studio, version 12.5.1, running on an Intel Core i7 up to 3.0 GHz machine with 8.0 GB of RAM. To obtain the Pareto efficiency curve an iterative model was also implemented in CPLEX by running the model for each weight combination regarding the two objective functions. The integrality gap obtained ranges from 0.00% to a maximum value of 4.97%, and the CPU time ranges from 0.53 to 1.12 seconds. The complete computational statistics is presented in Table 4.3.

Table 4.3 Computational Statistics

binary variables	integer variables	constraints	B&B nodes*	optimality gap (%)*	CPU time (seconds)*
3300	2800	153,272	71.67	3.10	0.87

* Average values for the 20 runs.

4.5.2.1. Pareto Frontier analysis (Step 3)

Considering the two objective functions ("Total Cost" and "Value Created") an approximation of the Pareto efficient frontier was determined by consistently changing the combination of weights in steps of 0.05. For each combination of weights, the MOIP is performed and a solution is obtained with the selection of a process design and the respective number of cycles for each product and period.

The determined Pareto front is depicted in Figure 4.6 in which is possible to see the relation between the "Total cost" (objective function 1) and the "Value created" (objective function 2). Through an immediate observation is possible to conclude that the "Value created" increases rapidly with the "Total cost" until a total cost value of approximately 40,000 rmu (reference monetary units). From this value there is no significant increase of the "Value crated" with the increase of "Total cost", meaning that no significant value is gained by changing over these solutions.

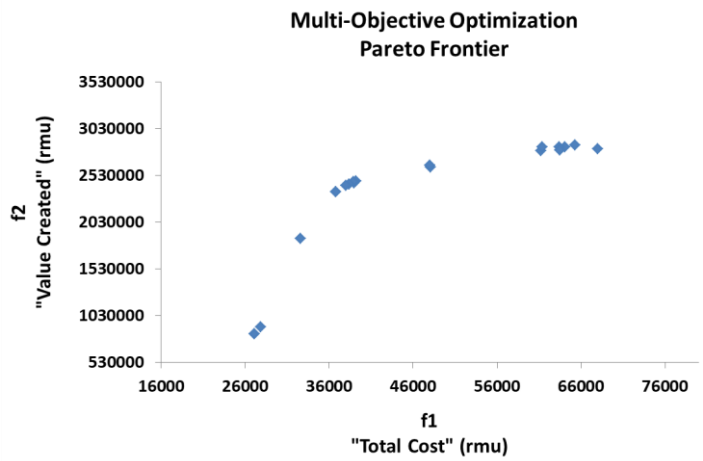


Figure 4.6 Pareto efficient frontier approximation.

4.5.2.2. Solutions performance assessment (Step 4)

For a better assessment of the solutions obtained in the Pareto frontier, a polynomial regression was used to adjust the respective values, and several lines with different slopes were determined (Figure 4.7). The slopes represent trade-off values between "Value created" and "Total Cost", measuring the Marginal Rate of Substitution (MRS) (Keeney & Raiffa, 1993), that is the rate at which the decision-maker is willing to pay to increase the "value created" or, in other words, how much he is ready to give up in "Value created" to gain in "Total cost". In Figure 4.7(b), 5 different trade-off values are represented, and is possible to observe that the higher the trade-off values are, the greater the variation of the "Value created" with the "Total cost". Thus, for a trade-off value of 150 the gain obtained in the "value created" with a small increase in the "total cost" is significantly larger than the one obtained for the trade-off value of 10, anticipating a possible region of good solutions for investment.

These lines are known as "indifference lines" (Keeney & Raiffa, 1993) since, for each one of them, there is a set of alternative solutions that have the same equivalent value for the decision-maker (utility), and so reflecting his preferences. Thus, different decisions-makers will have different indifference lines (i.e. lines with different slopes) revealing their preferences and risk attitudes (Keeney & Raiffa, 1993).

Nevertheless, the preferable solution in each trade-off (indifference) line will be the one that maximizes the decision-maker utility, corresponding to the tangency of the "Value created"/"Total cost" curve, and matching a Pareto optimal solution with a specific productivity level (Eq. (4.7)). For instance for a trade-off value of 250 the preferred solution has a total cost of approximately 27,000 rmu and a productivity level of approximately 30, while for a trade-off value of 50 the total cost is approximately 40,000rmu and the productivity level is 63, revelling a decision-maker more averse to risk in the second case (i.e. the decision-maker is willing to pay more to guarantee an higher productivity level).

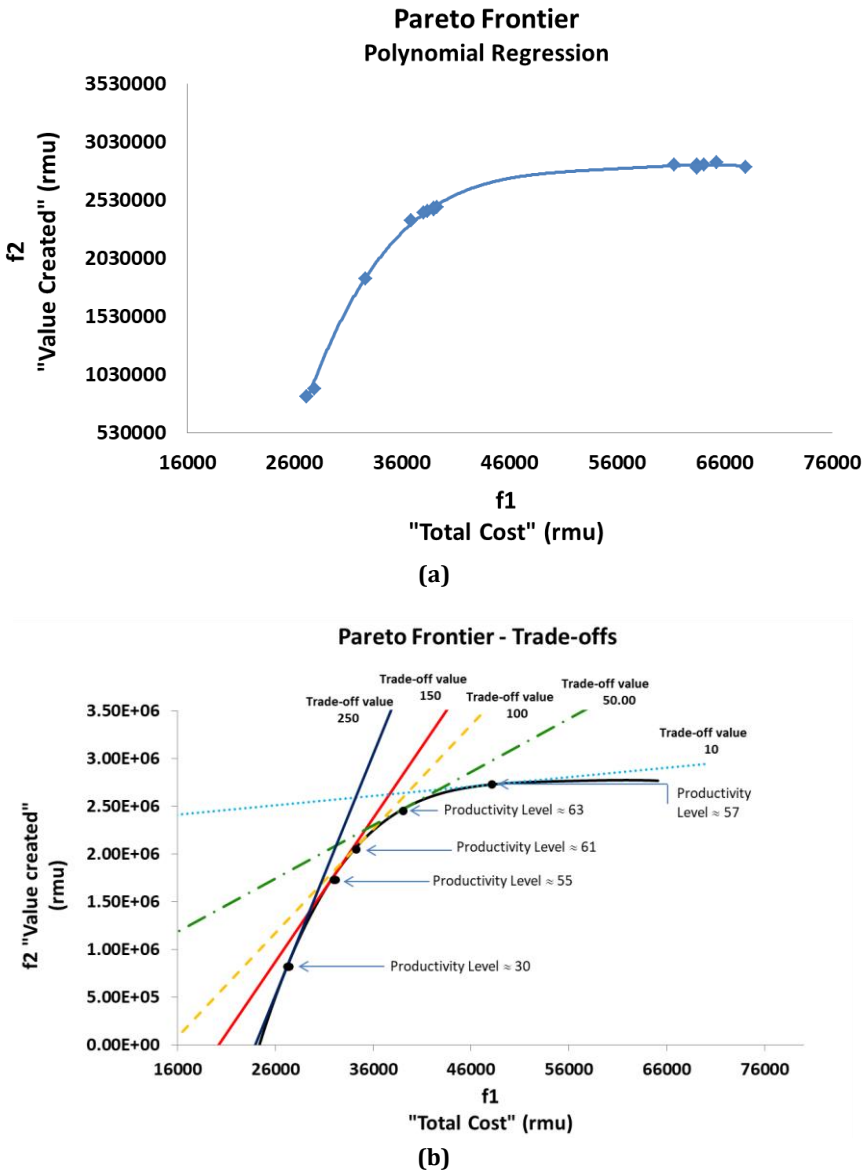
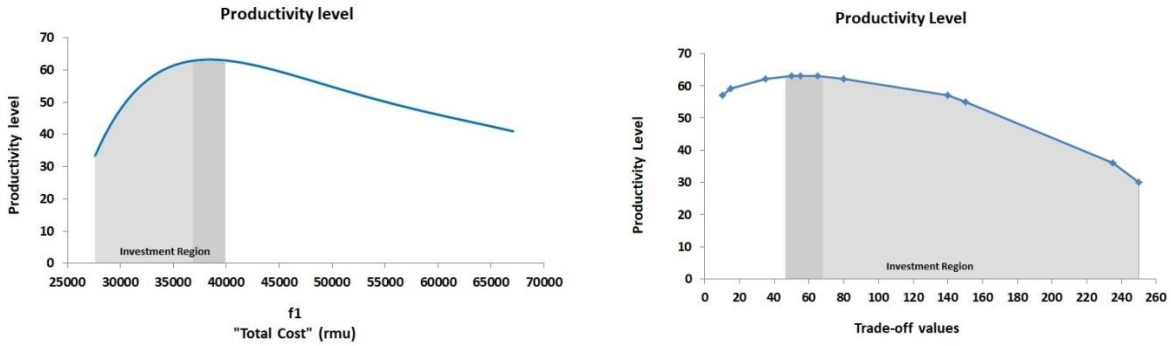


Figure 4.7 (a) Polynomial regression of the Pareto frontier, and (b) indifference lines for different trade-off values.

Moreover, according to Figure 4.7(b) despite the trade-off value of 250 be the one that provides greater "value created" increase with total cost, the productivity level is the lower one when compared to the other trade-off lines. This can better be seen in Figure 4.8(a) and Figure 4.8(b) in which the evolution of the productivity level with the "Total cost" and the "Trade-off values" respectively are depicted. According to Figure 4.8(a), the productivity level increases with an increase in total cost until a maximum productivity level of 63 from which increasing the total cost leads to a decrease in the productivity level. The same conclusion is possible to observe in Figure 4.8(b), although in this case it is important to notice that an increase in the trade-off value means a decrease in the total cost. This means that from a certain level of investment the "value" gained per unit of cost decreases, limiting the advantages of further investment.

Based on this analysis is possible to clearly determine the most attractive solution region for investment, as depicted in Figure 4.8(a) with the preferred investment region coloured in grey. Additionally, in an ideal setting in which uncertainty is absent from the decision process and investment resources are unlimited, the "best" solution is the one that falls in the dark grey region (Figure 4.8 (a) and (b)) where the productivity level reaches its maximum value. However, this is not the case in any real context, particularly for the pharmaceutical industry and its NPD process, and so a risk analysis should be performed combining the uncertainty factors and the decision-makers attitude toward risk.



(a) **(b)**

Figure 4.8 Productivity level variation with: (a) "Total cost", and (b) Trade-off values.

Risk analysis

The main goal of the present study is to determine the "best" design strategy (process design configuration) under uncertainty in product demand and clinical trial outcomes in order to prevent on one hand over investment that will increase the development costs that are already extremely high, and on the other hand delivery failures that will contribute to immediate loss of income for the products already in commercialization and a delay on the time-to-market for the under development products with future losses in revenue.

In that sense, risk as considered in this work is associated to the possibility of failing a delivery due to lack of production capacity associated to the design strategy adopted. Thus, a balance between the risk of delivery failure and the investment in production capacity should be made taking in consideration the decision-maker risk attitude. Figure 4.9 provides the relation between the "total cost" of a solution with its "capacity allocation", i.e. the production capacity that is available when selecting the specific solution associated with each trade-off value and productivity level. As expected, increasing the capacity allocation also increases the investment cost, and choosing higher trade-off values gives lower cost solutions, but also with lower flexibility and responsiveness to product demand variability due to the lower capacity allocation. In a highly uncertain context this means a higher risk of failing a delivery due to lack of available capacity to fulfil the current demand. Hence, the risk involved in these decisions reflects the likelihood of the production capacity

associated to a specific decision (i.e. process design) will not be sufficient to meet the uncertain future demand.

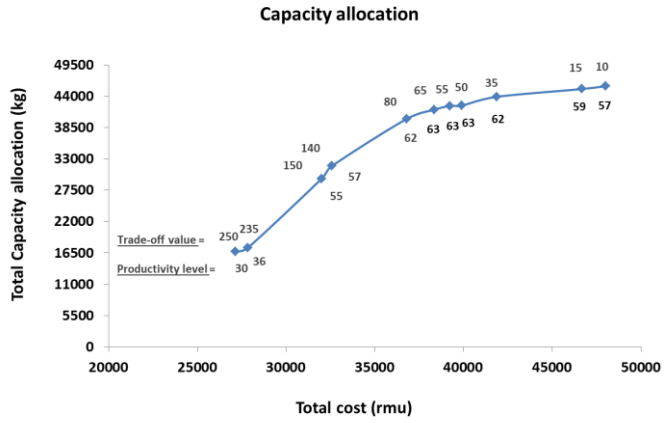


Figure 4.9 Relation between the capacity allocation and total cost expected for each trade-off value.

A comparison between the global production capacity allocation and the deterministic global product demand (aggregated values for all products and the entire planning horizon) is presented in Figure 4.10. Two extreme scenarios are considered: (i) considering that all under development products pass all clinical trial phases (extremely unlikely scenario), and (ii) considering that none of the under development products reach the market (more likely to occur). In this last scenario it is considered that all products will fail at the end of clinical trial phase I.

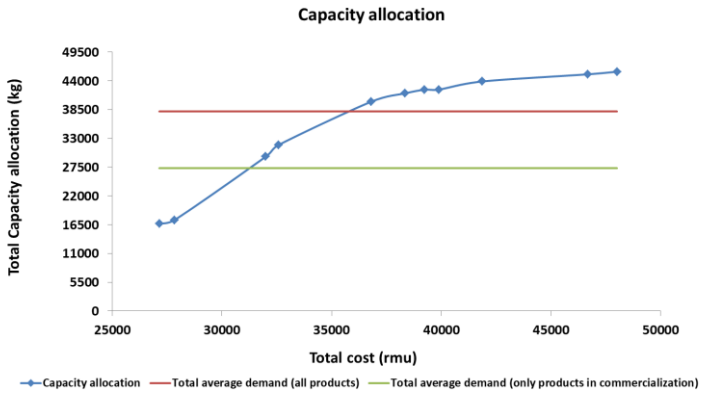


Figure 4.10 Relation between the capacity allocation and total cost expected for each trade-off value, and the deterministic values for the total product demand in two extreme scenarios: (i) considering that all under development products pass all clinical trial phases, and (ii) considering that none of the under development products reach the market.

Analysing Figure 4.10, and the two deterministic demand scenarios it become clear that any investment decision (i.e. design solution) below the value of ≈31,000 rmu is highly risky since with high probability it will not be able to accommodate the product demand associated to any product under development that may pass all the clinical trials. Also, the inherent variability of the product demand associated to the products already in commercialization may not be fully covered by design solutions under this value, and delivery fails may occur. On the contrary, solutions with a total cost

around 37,000 rmu or higher will probably result in a significant capacity excess due to the unlikelihood of all under development products reach the market. As a consequence, the total available capacity may not be entirely used, and the investment made will not be recovered. In this context, a decision-maker with high risk aversion will prefer to invest more in order to guarantee enough capacity to accommodate the production of all products even knowing that this will probably result in a strong suboptimal solution.

It is worth to notice however, that for this investment range (≈ 31,000-37,000 rmu), the respective productivity levels fall out of the dark grey region depicted in Figure 4.8. That is, within this range it will never be possible to achieve the solutions that yield the maximum productivity level. This may happen because the developed model doesn't make a distinction between capacity allocation and effective capacity utilization. Thus, all the available capacity in a specific solution determined by the MOIP model is converted in "Value created" by assuming full capacity utilization. Considering this, to be able to achieve the maximum values of productivity depicted in Figure 4.8, not only all the under development products need to reach the market, but also the respective product demands should be among the higher values possible according to each probability distribution curve.

Cost analysis

A cost analysis is performed in order to better understand the cost structure and the main contributions for the "Total cost" value. The Figure 4.11(a) presents the variation of the different cost contributions with the trade-off values, namely, the "variable cost", the "fixed cost" and the "process change cost". The "variable cost" seems to be the most relevant contributor to the total cost as the trade-off value increases. This can be explained by the fact that for each solution (selected process design) the "value created" can be increased by increasing the number of cycles of that process and consequently the amount of capacity that can be allocated for the same specific process design. However, for the lower trade-off values (below the value of 50) the "process change costs" seem to also assume a significant relevance. These values correspond to the most risk-averse attitudes, and therefore greater importance is given to the "value created" rather than to the "total cost". In this situation, the capacity increase is mostly driven by a change in the process design instead of a change in the number of cycles of the same process. On the other hand, above the trade-off value of ≈50 the process changes seem to be stable since above this value a higher importance is given to the "total cost" and a better balance is made between "process design" and "number of cycles". Additionally, in Figure 4.11(b) is depicted a comparison between the total cost variation with the trade-off values and the total cost obtained for the deterministic solution. The deterministic solution is obtained considering the expected average values for the product demands and considering that all under development products will reach the market (i.e. will successfully pass all clinical trials phases). Moreover, for the sake of comparison, the total cost of the deterministic solution only accounts for the variable, fixed and changeover costs (the inventory, waste, and investment costs were not considered for this analysis since they are not captured in the developed MOIP model). According to this figure (Figure 4.11(b)) above the trade-off value of ≈70 the total cost obtained considering the

developed approach (i.e. considering uncertainty) is always below the deterministic solution. It's interesting to observe that this trade-off value also corresponds approximately (being slightly above) to the upper limit for capacity allocation investment determined previously in Figure 4.10 in order to prevent over investment in capacity. Thus, solutions equal or below a trade-off value of 90 will be not only more costly, but also with an excess in capacity availability.

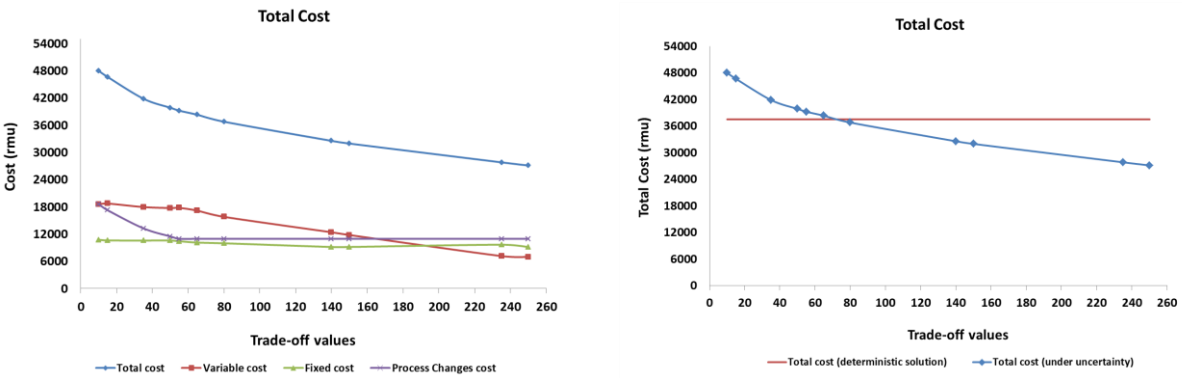
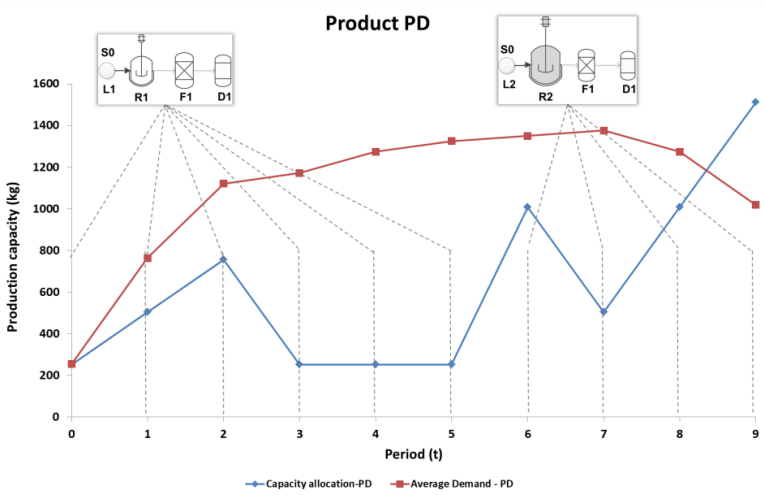


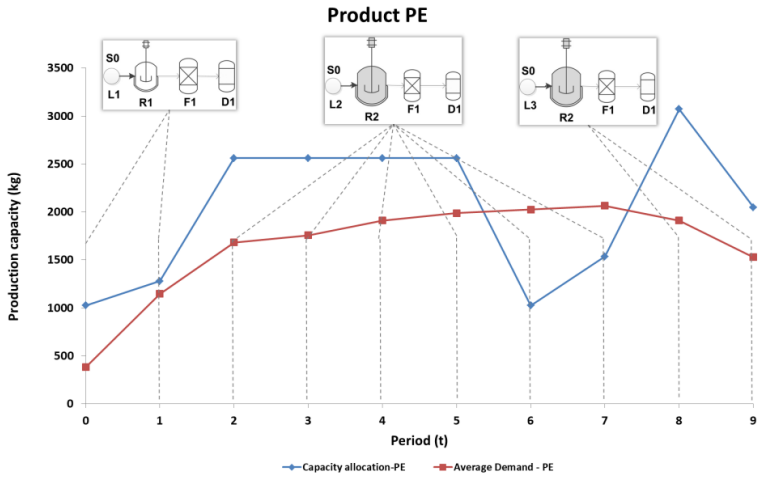
Figure 4.11 Total cost analysis for each trade-off value: (a) Total cost components (variable cos, fixed cost, and process changes costs); (b) Comparison between total cost obtained for each trade-off value and the total cost obtained in the deterministic solution.

4.5.2.3. Strategic final solution (Step 5)

The unique strategic final solution will be selected by the decision-maker taking into account the results obtained from the implementation of the unified decision-making framework depicted in Figure 4.4 and his own preferences and risk attitude. Therefore, based on the results and trade-off analysis presented in the above sections, and considering for instance a decision-maker with a more risk-prone attitude concerning the possibility of failing a delivery during the NPD process, the final decision may lay for instance on the trade-of values around 150 or 140 (Figure 4.9 and Figure 4.10). Selecting for example the value of 140 as the final solution to demonstrate the full implementation of the developed approach, the productivity level obtained is approximately 57 and the combination of weights associated to this solution is $\beta_1 = 0.85$ and $\beta_2 = 0.15$. The selected process designs and respective production capacities are depicted in Figure 4.12 (products in commercialization) and Figure 4.13(products under development) for each time period and product. As expected, for the under development products the capacity allocation after period t=2 (end of clinical trial phase I) is always under the average expected demand. Since the selected solution is closer to the scenario in which none of the under development products pass the clinical trials, the model only allocates a capacity safety level for each one of these products. Moreover, despite the fact that the available capacity is distributed among all products, the company may benefit from a capacity pooling system in which the unused capacity of one product is redistributed to the others as needed. In this way, if a product passes all clinical trial phases, it will still be possible to meet its expected demand.



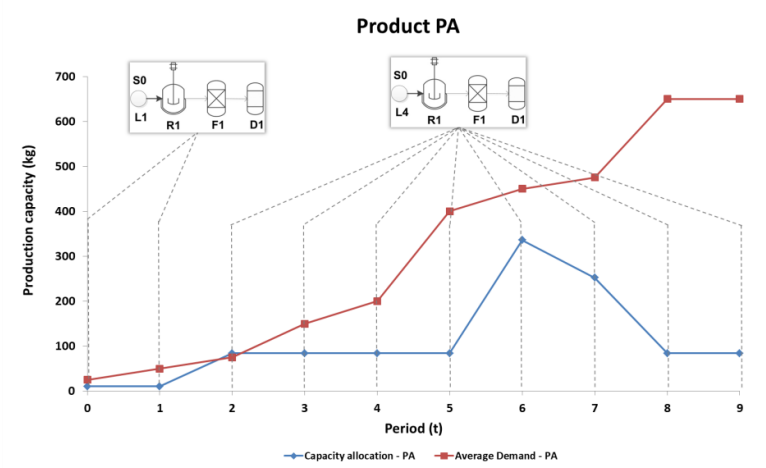
(a)



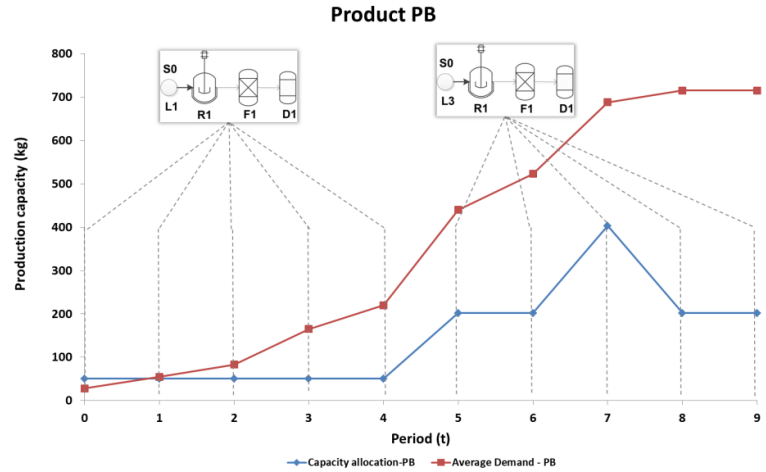
(b)

Figure 4.12 Results obtained for the capacity allocation considering a risk-prone decision-maker for the products already in commercialization.

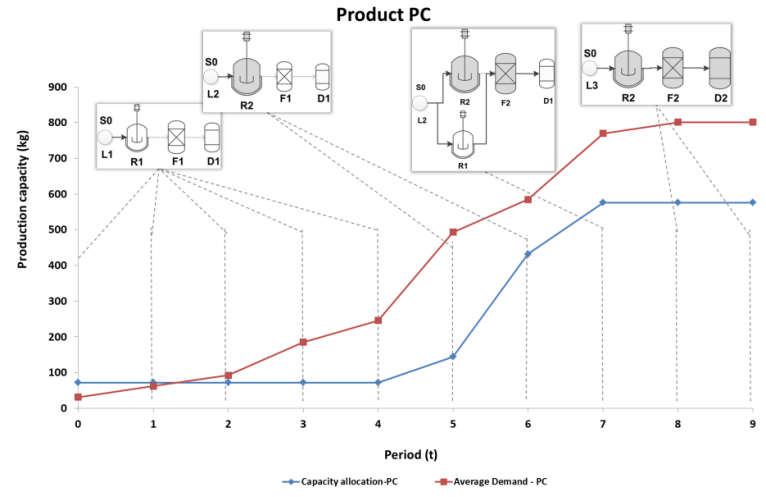
Regarding the products already in commercialization (Figure 4.12), for this level of investment, the model clearly favours the production of the most valuable product (that is product PE) by guaranteeing enough capacity to accommodate the average expected demand and its variability. Once again, in this case the unused capacity of one product may be used for the other by consolidating the available resources.



(a)



(b)



(c)

Figure 4.13 Results obtained for the capacity allocation considering a risk-prone decision-maker for the products under development.

In addition to this, and in order to deeply explore the application of the developed decision-making framework, the results obtained considering a risk-averse decision maker can be seen in Figure 4.14 and Figure 4.15 Figure 4.15. The solution obtained is for a trade-off value of 35 and a productivity level

of 62 (please refer to Figure 4.9 and Figure 4.10). In this case, the combination of weights associated to this solution is $\beta_1 = 0.46$ and $\beta_2 = 0.54$. A clear increase in production capacity is observed for all the products with the exception of product PA which presents an increase in the production capacity only in the last period when compared to the previous case. For the products already in commercialization the capacity allocation is almost always above the expected demand for both products, since these are the products that will guarantee a higher return for the company. On the other hand, for the products under development it is observed an approximation of the production capacity to the expected average demand (excepting for product PA). Considering that it is very unlikely that all products will reach the market, it is almost certain that not only all future production needs will be fully covered by this design solution, but also some overcapacity may be expected.

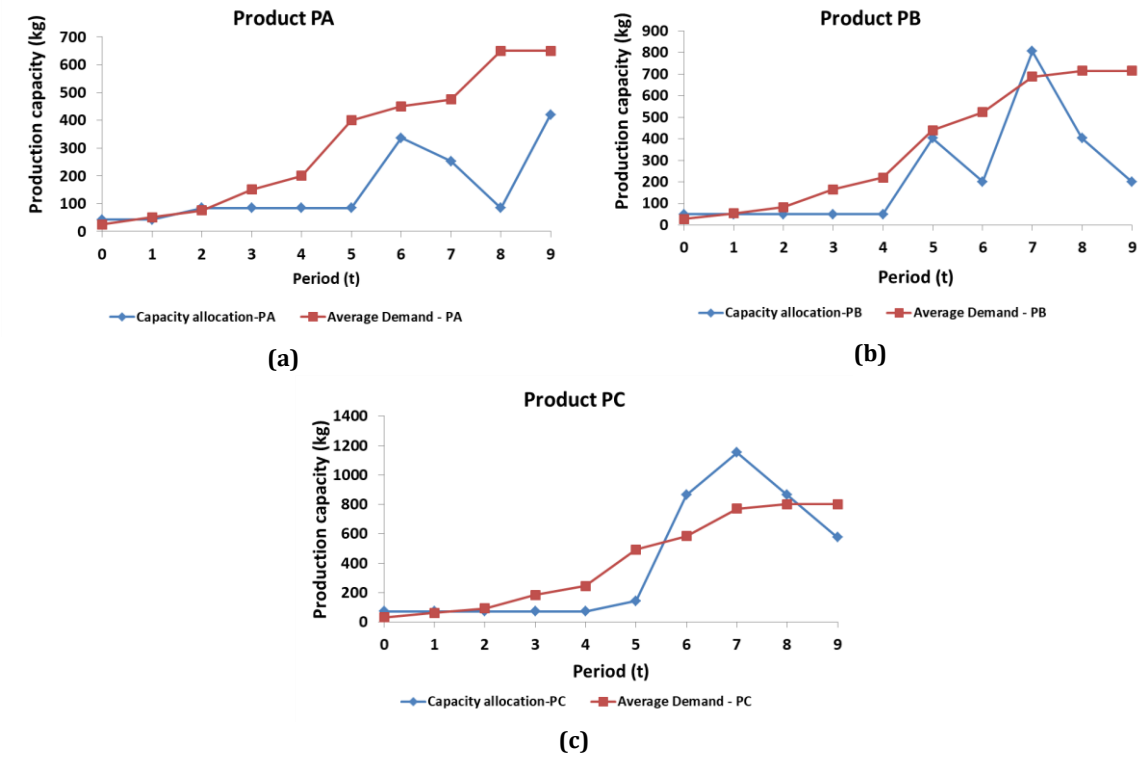


Figure 4.14 Results obtained for the capacity allocation considering a risk-averse decision-maker for the products under development.

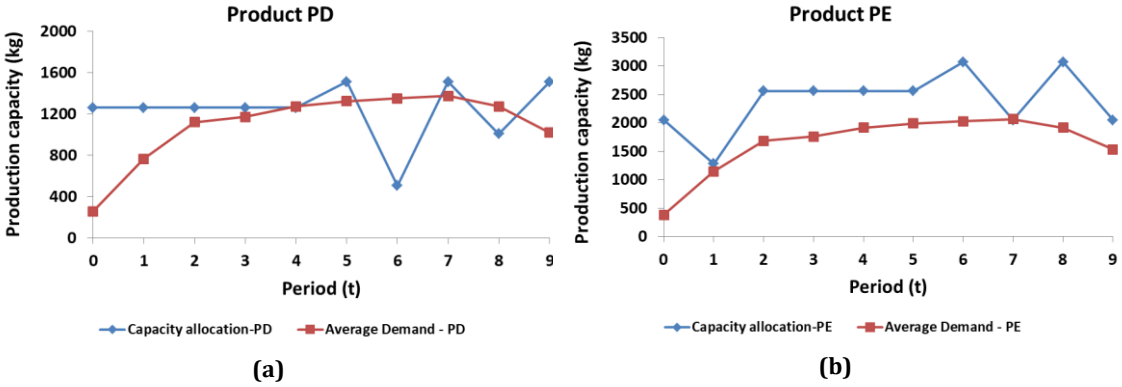


Figure 4.15 Results obtained for the capacity allocation considering a risk-averse decision-maker for the products already in commercialization.

Based on these results, obtained for two risk attitudes is possible to infer that not only the attitude toward risk, but also the level of investment that the company can afford has a great impact on the final solutions. A simple analysis of the Pareto optimal frontier is not sufficient to unveil the most adequate solution for the decision-maker or even for the company reality. Thus, the involvement of the decision-maker is crucial not only to impart a more realistic vision to the decision-making process but also to provide more meaningful solutions.

4.5.2.4. Dinkelbach's algorithm

In order to determine the unique optimal solution considering the maximization of the productivity as expressed in Eq. (4.8)), the Dinkelbach's algorithm was adopted by applying the algorithmic scheme presented in You et al. (2009).

The algorithm was implemented using IBM ILOG CPLEX Optimization studio, version 12.5.1, running on an Intel Core i7 up to 3.0 GHz machine with 8.0 GB of RAM. The algorithm was started by step 1 (please refer to You et al. (2009)) considering $q_2 = 0$, for $k = 2$ with k being the number of iterations (see Table 4.4).

The optimal value was obtained after 4 iterations and 36.14 sec, with a productivity level of 64.0185 (Table 4.4). Considering the multi-objective approach, the best value obtained for the productivity level was 63.3. The slight difference (≈1%) in these values can be explained by the fact that only an approximation of the Pareto frontier is obtained through the multi-objective approach and a subsequent polynomial regression is applied.

Nevertheless, when analyzing Figure 4.16 above, and considering the optimal solution obtained through the Dinkelbach's algorithm, we can say that a good approximation of the optimal Pareto Front was determined, and the final results are reliable and efficiently assessed through the proposed approach.

Moreover, as stated previously, the optimal solution may not reflect the real preferences of the decision-maker and his/her risk attitude toward uncertainty, and the rigorous assessment of this value is not the primary goal of this work.

Table 4.4 Dinkelbach's algorithm results

k (iteration)	$q_k = f2/f1$	***f2*** ***("Value Created")***	***f1*** ***("Total Cost")***	$F(q_k)$
2	0.0000	2.80×10^6	1.04×10^5	2.80×10^6
3	26.9816	2.45×10^6	3.86×10^4	1.41×10^6
4	63.4473	2.41×10^6	3.77×10^4	2.14×10^4
5	64.0185	2.41×10^6	3.77×10^4	2.45×10^4
6	64.0185	2.41×10^6	3.77×10^4	2.45×10^4

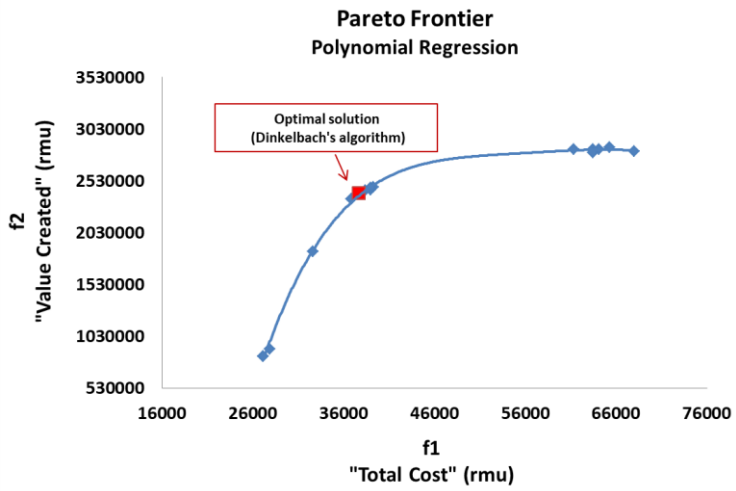


Figure 4.16 Optimal solution obtained by implementing the Dinkelbach's algorithm.

4.6. Conclusions

In this chapter an extension of the proposed TSMCS framework is presented in order to complete the development of a new unified decision-making framework to address the stochastic product launch planning problem (including process design and capacity planning decisions) in the chemical-pharmaceutical industry. The first part of the framework depicted in Figure 4.4 (Step 1 and 2) is developed in the previous chapter (chapter 3) by generating the complete set of solutions, considering uncertainty in product demand (for both types of products) and in the clinical trials outcomes (for the under development products). The most frequent process design solutions were then obtained and defined as part of the set of candidate possible final solutions considered here.

In the present work, the focus is given to the determination of the unique design strategy to follow (the stochastic process design solution) through the development of a Multi-Objective Integer Programming (MOIP) model, embedded in the unified decision-making framework presented in Figure 4.4 (Steps 3, 4 and 5), in order to "maximize" productivity by balancing two conflicting objectives. The final solution is determined by explicitly considering the decision-maker preferences and attitude toward risk, filling the existing gap associated to the current paradigms to tackle uncertainty in which a unique optimal prescriptive decision is obtained. Given the highly strategic nature of the decisions considered here, the involvement of the decision-maker in the final solution is critical and its importance is highlighted through the obtained results.

The developed MOIP model has proven to be efficient and effective in selecting the final solution, while the multi-objective approach allowed to explicitly considering the decision-maker risk attitude by obtaining an approximation of the Pareto-front. This, allowed the decision-maker to ponder all possibilities and trade-offs between the two objective functions (indifference lines) before selecting the final solution. Nevertheless, the selection of a single solution from the Pareto set is not a straightforward process or even sufficient to determine the most suitable solution for the decision-

maker. Therefore, a subsequent Pareto analysis is performed with the assessment of the solutions performance (productivity level) and risk analysis (likelihood of failing the future production needs).

The results obtained clearly show how the different trade-off values (indifference lines) reflects different attitudes towards risk, and how these different risk attitudes influence the final solution. A good balance between investment and capacity allocation has been achieved by the model according to the different decision-maker preferences. Additionally, interesting results were also obtained for the productivity level by clearly determining the most promising solutions region for investment.

Finally, the complete unified decision-making framework developed has proven to be a robust and reliable tool to address the highly stochastic product launch planning problem in the pharmaceutical industry. On one hand, the framework clearly identifies the most promising process designs and scale-ups that maximize profit (NPV) under uncertainty by mapping a wide range of possible future scenarios. On the other hand, the final design strategy is determined based on the most promising process design candidates, and considering the decision-makers risk attitudes, to "maximize" pharmaceutical productivity. Moreover, the optimal solution of Dinkelbach's algorithm shows that the results obtained through the multi-objective approach are robust and reliable.

The final solution obtained at the early stages of the product development enables on-time decision-making, while balancing the total investment and the production capacity allocation in order to achieve simultaneously three main goals: (i) prevent over investment; (ii) guarantee sufficient production capacity to fulfil all future product demand needs; and (iii) minimizing process design changes over the development process, by benefitting from a better management of the available capacity (through capacity pooling methods).

Finally, when compared the proposed unified decision-making framework to the most widely used TSSP approaches, some advantages can be outlined, such as: (i) the ability to generate a wide range of possible realizations, considering several uncertainty parameters simultaneously, without increasing the model size and complexity; (ii) the ability to efficiently capture the binary nature of the clinical trials outcomes uncertainty; and (iii) the ability to incorporate the decision-maker preferences in the final solution, making it more robust and reliable.

5. Conclusion

In this chapter the conclusion of this thesis is presented highlighting the main research contributions and recommendations for future development.

5.1. Research contributions

In this work, the complexity of the pharmaceutical industry and its operations are investigated with the main objective to contribute to the improvement of the global efficiency. For this purpose, we attempted to provide answers to the three formulated research questions. In a first step, the major industry's distinctive features, as well as its current state, operational fragilities, and research gaps are identified and thoroughly analysed (chapter 2). The general structure of the expected future pharmaceutical supply chain is outlined and, based on this, a comprehensive decision-making reference framework is proposed.

In a second step, the stochastic product launch planning problem is addressed through the development of effective optimization-based approaches. An innovative two-step Monte Carlo simulation framework is then presented to determine the integrated process design and production planning decisions under uncertainty (chapter 3). Following this, a Multi-Objective Integer Programming model is developed to obtain the final strategic solution and complete the unified decision-making framework (chapter 4).

Despite the detailed findings are already clearly described in each one of the chapters mentioned above, the major contributions achieved by this research work (for both practitioners and researchers) can be outlined in two different levels of analysis, as depicted in Figure 5.1.

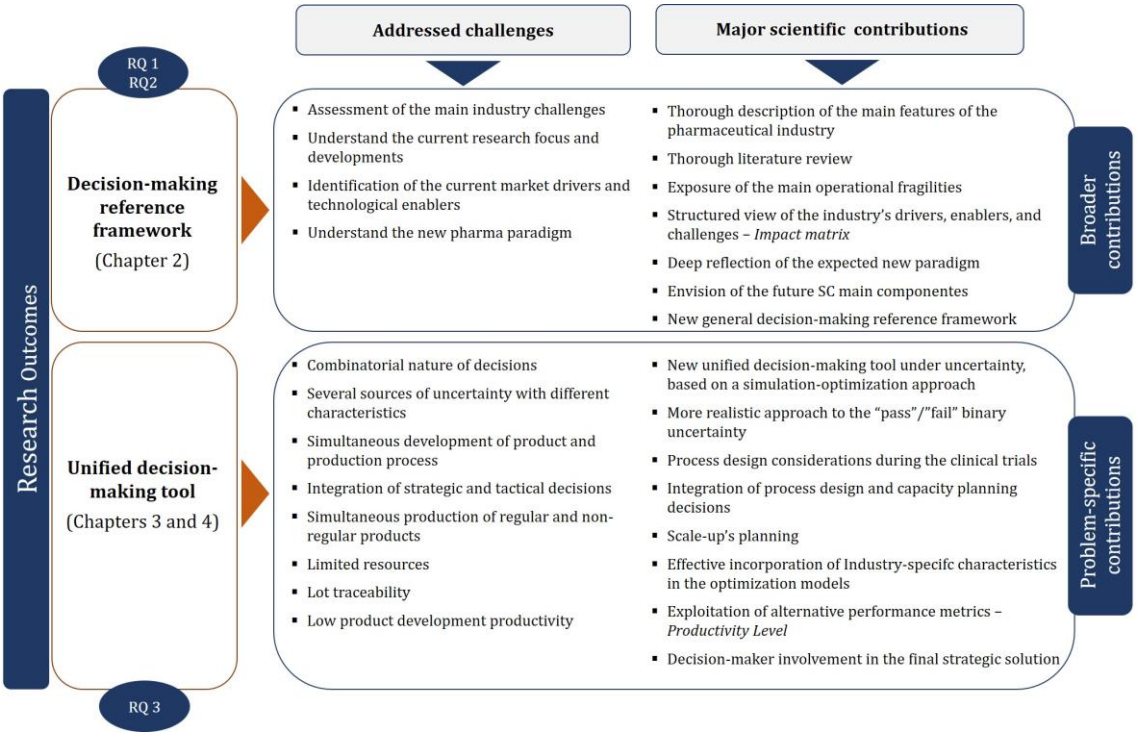


Figure 5.1 Addressed challenges and major contributions of the thesis.

At a broader level, the materialization of the expected new paradigm into a structured view of the future supply chain (and its main components), reflects one of the first attempts to envision objectively the operational implications of the current market and technological pressures. It is clear

that the old paradigm of the industry is no longer effective and companies, although discretely, are just starting to adapt by redefining its strategies and operational practices.

On the other hand, the identified planning problems and solution approaches addressed in the literature unveil a still very narrow perspective from academia, demonstrating an overall misalignment with the main trends driving the industry.

This highlights the notion that the changes imposed by the current business context are not only extremely ambitious, but also disruptive in the context of a highly traditional and conservative industrial sector, as it is the pharmaceutical industry. An effective change to a greater centrality of the patient together with the adoption of innovative technologies and decision-making tools is a highly complex and lengthy process, with the industry just starting to take its first steps. Main findings, however, also disclosure the most pressing needs related to the improvement of operational efficiency across the entire product life-cycle activities, particularly for the drug development process. Reducing not only the time-to-market, but also the overall supply chain costs are gradually becoming as important as quality assurance goals.

In this way, at a narrower (problem-specific) level, important contributions were made regarding the approximation between optimization-based approaches and real settings by effectively incorporating industry-specific features into the developed models (see Figure 5.1). On one hand, the proposed simulation-optimization approach introduces an innovative way of dealing with several sources of uncertainty with very different inherent behaviours while, at the same time, providing a structured way to search for the optimal solutions. This methodology has proven that is possible to efficiently tackle uncertainty without using complex and large-scale multi-stage stochastic programming models. Moreover, the integration of production/capacity planning with process design decisions during clinical trials represents also an important contribution. Not only, because the strategic/tactical decision-levels integration is explored, but also due to the relevance of process design considerations during product development.

On the other hand, the unique final strategic solution is determined through a multi-objective approach explicitly incorporating the decision-maker preferences, which are still very poorly explored in the literature, despite its practical relevance. Also, the exploitation of alternative performance metrics, such as the productivity level, to guide the final strategic decisions, adds an essential contribution to the current literature which has been highly focused on strictly profit goals.

Overall, this work has contributed to bring the academia closer to industry by understanding its needs and converting them into decision-making requirements and novel modelling features.

Figure 5.1 depicts not only the major contributions, but also the main challenges that have been addressed and have driven the further development of this work.

5.2. Future research work

The main findings detailed in each chapter of this thesis already point to some of the possible future research paths. Nevertheless, supply chain and operational management within the pharmaceutical context is a fruitful area of development, worthy a more deep reflexion. In this way future recommendations for development will be presented following two lines of action.

The first one dedicated to natural extensions of the developed methodologies, and the second one, more focused on general considerations regarding the pharmaceutical operational context.

Further extensions

1. *Alternative demand patterns.*

   As highlighted in this work, uncertainty plays a fundamental role in the NPD process. Exploring alternative ways of representing it will contribute to improve the analysis and enhance the methodology value. Thus, it would be interesting to evaluate not only different demand patterns, but also alternative distribution functions reflecting different behaviours regarding patient enrolment to trials (for products under development) or patient adherence to treatments (for products in commercialization).

2. *Multi-echelon approach*

   The ability to produce and deliver the right quantities at the right time to the clinical sites is paramount to reduce the time-to-market. In that sense, further developments should include an extended analysis of the problem integrating the manufacturing component with the packaging and distribution functions. This will require the development of effective large-scale formulations to deal simultaneously with process design, production/capacity planning, and inventory management decisions across the entire clinical trials supply chain.

3. *Dynamic portfolio considerations*

   In a typical pharmaceutical company, the portfolio pipeline is composed by several products at different stages of development. During the development period some products are abandoned, while new ones may be added to the portfolio. This dynamic behaviour is not fully captured in this work, as it is considered (for the sake of clearness) that all the products reach clinical trial phase I at the same time. In this way, it would be interesting to explore more deeply this issue by a generalization of the model to account for this dynamic behaviour.

New research areas

1. *Functional integration*

   It is observed a lack of research exploring holistic approaches able to capture the full integration between the clinical development, product launch activities, and commercial

distribution. This is a fruitful area of development considering the modelling challenges involved and the expected operational gains for the industry.

2. *Multi-objective approaches*

   The literature assessment reveals a mature development of optimization-based approaches focused on single objectives based on profit or cost metrics. The complexity of the planning problems in the pharmaceutical context, however, encompass a much wider range of dimensions and performance indicators. Therefore, there is high potential for the exploitation of multi-objective approaches accommodating novel performance metrics based on economic, environmental and social dimensions.

3. *Exploitation of market and technological trends*

   As described in chapter 2, major technological (continuous manufacturing and digital capabilities) and market (personalization) trends are currently changing the pharmaceutical industry. Despite its impacts on decision-making tools, these changes are still seldom considered in the current modeling approaches. Exploring these new features within a modelling perspective (e.g. redefining variables or constraints) will be critical for the decision-making process and, undoubtedly, a promising area of future development.

Appendices

Appendix A – Decision-levels hierarchical representations proposed in the literature

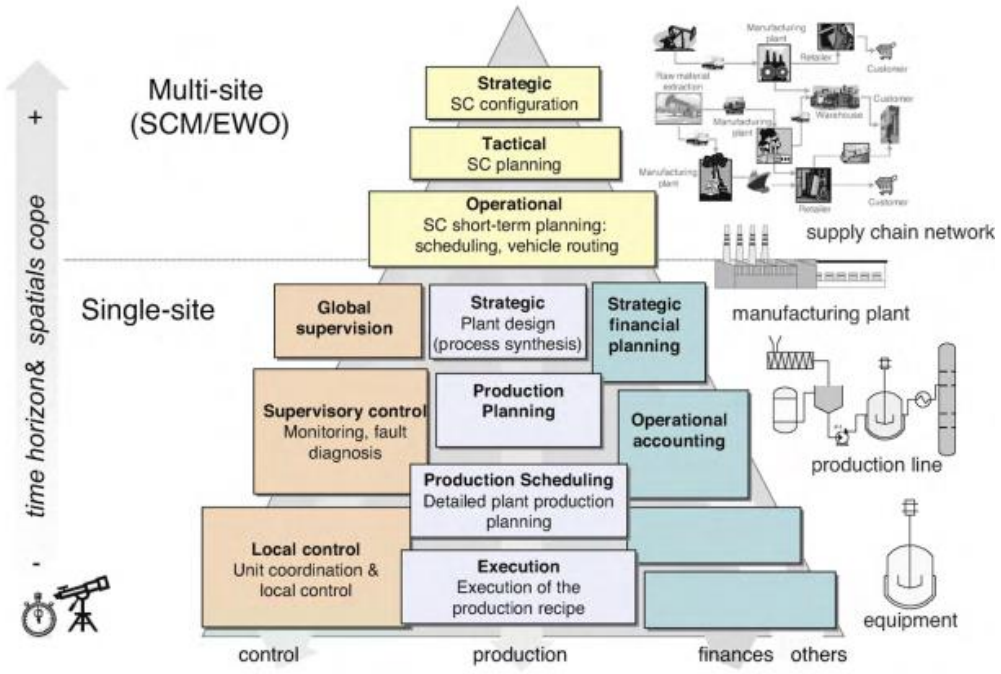


Figure A.1 Hierarchical structure of decision problems in the PSE community (Grossmann & Guillén-Gosálbez, 2010)

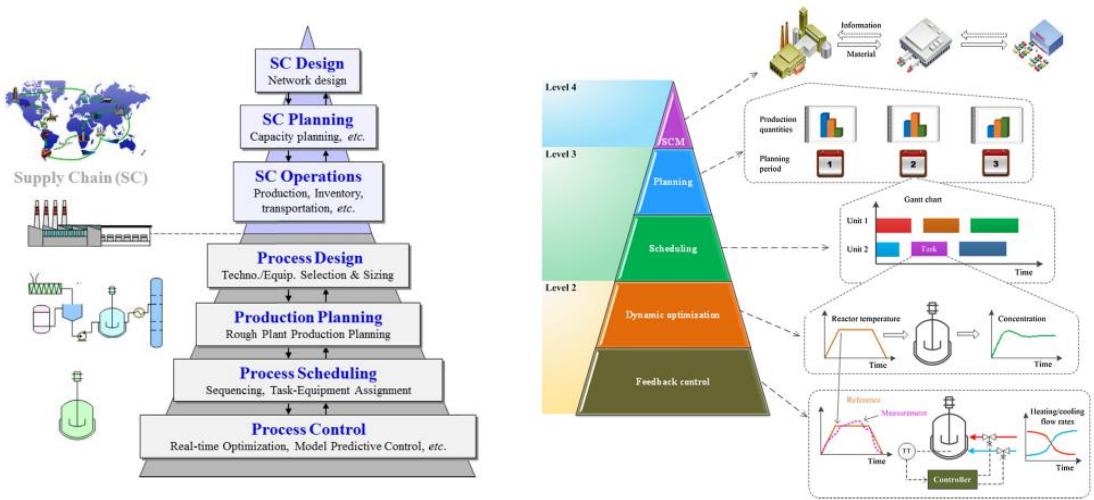


Figure A.2 Hierarchical structure of decision problems (a) presented by Garcia & You (2015); and (b) presented by Chu & You (2015)

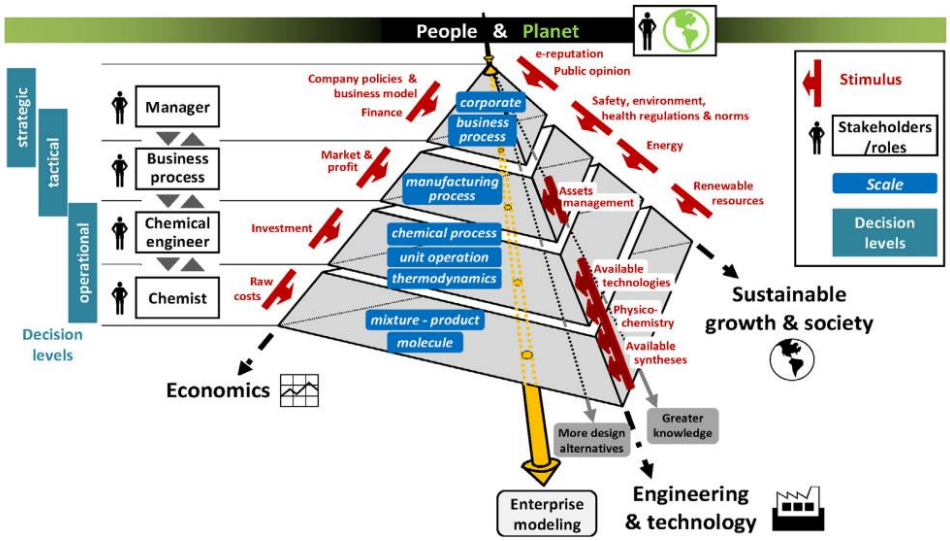


Figure A.3 Chemical enterprise modeling framework (Heintz et al., 2014)

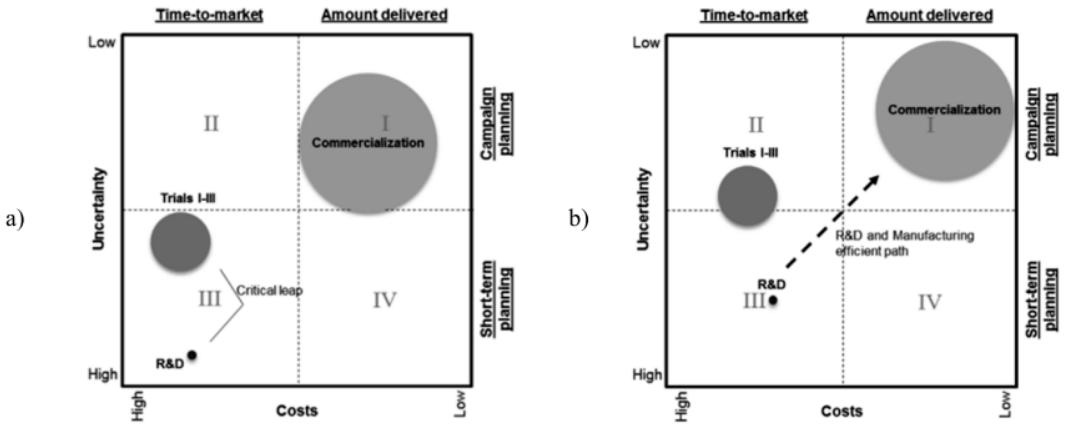


Figure A.4 Delivery Trade-offs Matrix (Moniz et al., 2015a)

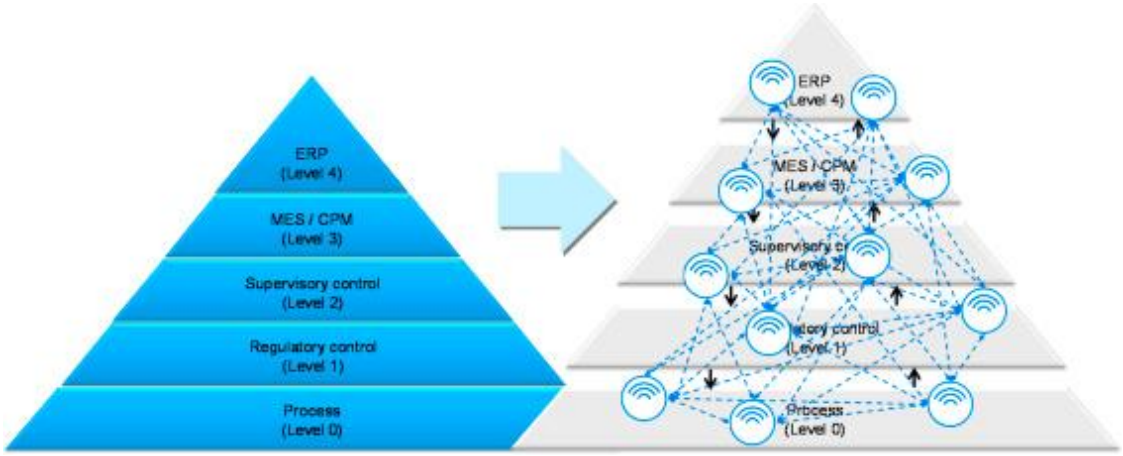


Figure A.5 Decision-levels integration (Harjunkoski, 2017)

Appendix B – Literature review

Table B.1 Main problems in the pharmaceutical industry addressed in the PSE and management literature

Functional area	Main problem	Sub-problem	# papers	U(1)	Publications
R&D / Product Development	Portfolio Management	Portfolio selection	20	S	(Subramanian et al., 2000; Subramanian et al., 2001); (Maravelias & Grossmann, 2001); (Blau et al., 2000); (Rogers et al., 2002); (Subramanian et al., 2003) (Blau et al., 2004a); (Gupta & Maranas, 2004) (Rajapakse et al., 2005); (Charalambous & Gittins, 2008); (George & Farid, 2008; George & Farid, 2009); (Zapata et al., 2008; Zapata & Reklaitis, 2010); (Pérez-Escobedo et al., 2011); (Perez-Escobedo et al., 2012); (Hassanzadeh et al., 2014); (Christian & Cremaschi, 2015; Christian & Cremaschi, 2017); (Zeng & Cremaschi, 2017)
				D	-
		Scheduling of testing tasks / resource allocation	29	S	(Schmidt & Grossmann, 1996b); (Schmidt & Grossmann, 1996a); (Subramanian et al., 2000); (Subramanian et al., 2001); (Blau et al., 2000); (Maravelias & Grossmann, 2001); (Subramanian et al., 2003) (Blau et al., 2004a); (Choi et al., 2004); (Gupta & Maranas, 2004); (Colvin & Maravelias, 2008; Colvin & Maravelias, 2009; Colvin & Maravelias, 2010; Colvin & Maravelias, 2011); (George & Farid, 2008; George & Farid, 2009); (Zapata et al., 2008; Zapata & Reklaitis, 2010); (Varma et al., 2008a); (Pérez-Escobedo et al., 2011); (Perez-Escobedo et al., 2012); (Hassanzadeh et al., 2014); (Christian & Cremaschi, 2015; Christian & Cremaschi, 2017); (Zeng & Cremaschi, 2017); (Christian & Cremaschi, 2018)
				D	(Schmidt et al., 1998); (Jain & Grossmann, 1999); (Maravelias & Grossmann, 2004)
	Clinical trial Supply Chain operations	SC design/ capacity planning	5	S	(Farid et al., 2005) (Chen et al., 2012a); (Chen et al., 2012b), (Fleischhacker et al., 2015), (Marques et al., 2017b)
				D	-
		Production/ inventory planning	7	S	(Peterson et al., 2004); (Abdelkafi et al., 2009); (Fleischhacker & Zhao, 2011); (Chen et al., 2012a); (Chen et al., 2012b); (Fleischhacker et al., 2015); (Marques et al., 2017b)
				D	-
		Scheduling	0	S	-
				D	-
Supply Chain Operations	Product Launch / New product introductions	Portfolio selection	8	S	(Rotstein et al., 1999); (Maravelias & Grossmann, 2001); (Gatica et al., 2003b; Gatica et al., 2003a); (Levis & Papageorgiou, 2004); (Tsang et al., 2007a; Tsang et al., 2007b)
				D	(Papageorgiou et al., 2001)
		SC design/ capacity planning	15	S	(Rotstein et al., 1999); (Maravelias & Grossmann, 2001); (Gatica et al., 2003b; Gatica et al., 2003a); (Levis & Papageorgiou, 2004); (Wan et al., 2006b); (Tsang et al., 2007a; Tsang et al., 2007b); (Laínez et al., 2009b); (Sundaramoorthy et al., 2012); (Kaminsky & Yuen, 2014)

Functional area	Main problem	Sub-problem	# papers	U(1)	Publications
				D	(Papageorgiou et al., 2001); (Sundaramoorthy & Karimi, 2004); (Naraharisetti & Karimi, 2010); (Hansen & Grunow, 2015a)
		Production / inventory planning (single- and multi-site)	13	S	(Maravelias & Grossmann, 2001); (Gatica et al., 2003b; Gatica et al., 2003a); (Levis & Papageorgiou, 2004); (Tsang et al., 2007a; Tsang et al., 2007b); (Laínez et al., 2009b); (Sundaramoorthy et al., 2012); (Hansen & Grunow, 2015b)
				D	(Papageorgiou et al., 2001); (Sundaramoorthy & Karimi, 2004); (Naraharisetti & Karimi, 2010); (Hansen & Grunow, 2015a)
	Global Supply Chain and Manufacturing	SC design/ capacity planning	13	S	(George et al., 2007); (Mousazadeh et al., 2015); (Seifert et al., 2015); (Zahiri et al., 2017)
				D	(Grunow et al., 2003); (Sousa et al., 2008); (Nagurney et al., 2013); (Friemann & Schönsleben, 2016); (Liu & Papageorgiou, 2013); (A. Narayana et al., 2014); (Weraikat et al., 2016); (Banimostafa et al., 2015); (Low et al., 2016)
		Production / inventory planning	30	S	(Stefansson et al., 2006; Stefansson et al., 2009); (Lakhdar et al., 2006; Lakhdar & Papageorgiou, 2008); (Mousazadeh et al., 2015); (Assid et al., 2015); (Jia & Zhao, 2017); (Amaro & Barbosa-Póvoa, 2006); (Amaro & Barbosa-Póvoa, 2009); (Linninger et al., 2000; Linninger & Chakraborty, 2001); (Nematollahi et al., 2017; Nematollahi et al., 2018)
				D	(Gupta et al., 2002); (Berning et al., 2002); (Grunow et al., 2003); (Sundaramoorthy et al., 2006); (Meijboom & Obel, 2007); (Sousa et al., 2008; Sousa et al., 2011); (Ruiz-Torres et al., 2010); (Susarla & Karimi, 2012b);(Liu et al., 2014); (Moniz et al., 2014a); (Meiler et al., 2015); (Vieira et al., 2016); (Liu & Papageorgiou, 2013); (Lücker & Seifert, 2017); (Amaro & Barbosa-Póvoa, 2008); (Su et al., 2017)
		Production scheduling	26	S	(Stefansson et al., 2006; Stefansson et al., 2009); (Eberle et al., 2014); (Baumann & Trautmann, 2014); (Pistikopoulos et al., 2015);
				D	(Graells et al., 1998); (Raaymakers & Hoogeveen, 2000); (Roslöf et al., 2001); (Berning et al., 2002); (Amaro & Barbosa-Póvoa, 2005); (Castro et al., 2008); (Ciavotta et al., 2009); (Venditti et al., 2010); (Kopanos et al., 2010); (Stefansson et al., 2011); (Kabra et al., 2013); (Moniz et al., 2012; Moniz et al., 2013a; Moniz et al., 2014a; Moniz et al., 2014c); (Meiler et al., 2015); (Costa, 2015); (Vieira et al., 2016); (Eberle et al., 2016); (Amaro & Barbosa-Póvoa, 2008); (Halim & Srinivasan, 2011)

(1) **Uncertainty: S –** Stochastic; **D –** Deterministic.

Appendix C – Technology enablers

Table C.1 Technology enablers and key features

	Tech. trends	Technology key features/capabilities	Potential impacts on PSC	Adoption barriers	Adoption enablers
PRODUCT	**Cell and Genetic Therapies**	Development of personalized medicines	- New patient-centric business models - Increased product value - Higher product variability and volume mix - Reduced clinical trials dimension - Reduced product development cycle time - Increased technical success during product Development *Patients are selected based on specific genome characteristics*	- Scientific development - Lack of regulatory protocols and regulations to guarantee quality and patients safety	- Encouragement and support from regulatory agencies (FDA, EMA) - Enhanced R&D productivity - Reduced time-to-market
		Development of innovative drugs to target unmet needs (e.g. Orphan Drugs)	- New business models based on niche markets - Higher product variability and volume mix - Faster product development cycles and extended patent protection (due to the incentives from regulators)	- Small market - less economically attractive for companies	- Programs already implemented by regulators (FDA and EMA) with incentives for the prioritization of the development of drugs targeting rare diseases

	Tech. trends	Technology key features/capabilities	Potential impacts on PSC	Adoption barriers	Adoption enablers
PROCESS	**Continuous manufacturing**	Seamless (continuous) production, eliminating holding times between the "stop-and-start" steps of the traditional batch production;	- More responsive SC → Demand-driven supply - Shorter lead times; - Reduced Inventory Levels - Reduces variability between individual batches and the risk of adverse events (Martin, 2016) - Improved quality with less rework - Reduced overall operational costs and safety - Reduced product development cycle time and costs	- Concerns about validation and approval - Mind-set readiness - Initial investments costs - Higher technical complexities in the design and operational phase - The need for a total redesign for the marketed products originally designed for batch production - Current inventory of batch facilities that are dimensioned for blockbuster's production - Current lack of vendors of reliable process equipment compatible for continuous manufacturing	- Encouragement and support from regulatory agencies (FDA, EMA) - More cost-effective technology demonstrated by academia and practitioners - Already adoption by some big players - Risk of being outpaced by competitors
		Reduction in manufacturing footprint (Small equipment and space required)	- Smaller-scale processing units to manufacture similar quantities (when compared to batch units) - Reduced management burden - Reduced inventory levels, particularly for intermediates - Shorter lead times and higher throughputs - Reduced production and distribution costs		
		Production of various scales with a given process due to its continuous nature as opposed to the discrete nature of batch sizes	- Production flexibility (product/volume mix) - Improved responsiveness to market dynamic - Improved adaptability to different regional markets - Easy scale-up during product development and market launch (Daszkowski, 2013) - Better matching between production, inventory and market demand needs		
		Better process understanding	- Enable the identification of critical points affecting quality and the design of quality control strategies to address these critical points - Enable fundamental process understanding earlier in development phase		
		Higher degree of automation and real-time monitoring	- Enhanced process robustness and reliability - Real-time monitoring and control - Prevention of human errors - Enhanced quality and process control - Delivery of "Right-first-time" quality → Less rework -- Reduced inventory - Preventative/predictive maintenance and condition monitoring.		
		Higher operational efficiency	- Higher throughput - Higher process yields - Better resources and energy utilization → reduced environmental impact - Higher capacity utilization (OEE)		

Tech. trends	Technology key features/capabilities	Potential impacts on PSC	Adoption barriers	Adoption enablers
Digitalization (Industry 4.0)	Data-driven integrated systems	- New data-driven business models; - Democratization of information in a real-time flow of data (patient data, product data, process data, and supply chain operations data) - Data-driven decision models focused on the patient and customization - Drug development based on update patient data → increased probability of technical success and of the perceived value for the enrolled patients - Reduced clinical trials dimension and costs - Reduced drug development cycle times	- Need for greater understanding of the manufacturing processes - Requirement of accurate online sensing of key product and process parameters including closed-loop control and online optimization - The current level of automation is low - The current virtual manufacturing technology is absent - Traditional practices based on batch operating mode → the transition to continuous manufacturing is essential to the adoption of industry 4.0 capabilities - Need for global standards and data sharing protocols - Safety, data security and data ownership → intellectual property data and particularly important the health patient data due to its sensitivity and confidentiality issues.	- Wide range of process sensors installed, and available parameters data along the process plant - Some process industry key players already developing research programs based on Industry 4.0 paradigm
	Cyber-Physical-Systems	- Self-organising and reconfigurable SC in which goods, machines, and organizations are connected to each other; - Decentralized decision-making processes; - New product-service solutions (e.g. novel packaging solutions that facilitate patient compliance and adherence to treatment) - Advanced simulation and optimization models - Move from mass-production to mass-customization - Flexibility and self-adaptation of the ongoing clinical trials to the patient needs - Reduced clinical trials dimension and costs - Reduced drug development cycle times		
	Real-time monitoring	- Real-time flow of data (patient data, product data, process data, and supply chain operations data) - Better process control and adaptability to sources of variability → improved quality - Real-time anticipation and self-reconfiguration to react to market disruptions - Real-time adjusting of process parameters throughout the manufacturing process → reducing waste and improving production yields. - Improved quality through predictive analytics		
	Enhanced process safety and predictive maintenance	- Self-aware production lines constantly monitoring themselves and reporting on their own condition - Reduced reactive maintenance - Improve capacity utilization - Improve process safety - Reduced production costs		
	Enhanced "track-and-trace" capabilities	- Critical for the personalized SC - Reconfigurable and adaptive supply chain around the patient, based on remote patient diagnostic data - Improved end-to-end visibility and efficient communication between all SC entities → better control of counterfeit drugs - Enhanced visibility across the entire clinical trial supply chain with improved communication between all stakeholders involved, including the patient.		

	Tech. trends	Technology key features/capabilities	Potential impacts on PSC	Adoption barriers	Adoption enablers
DECISION-MAKING	**Decision-making**	Enhanced modelling, optimization and decomposition schemes	- Improved decision-making capabilities - Effective integration across company functions, physical organisations and decision-making levels - Effective incorporation of uncertainty arising at different scales - Effective incorporation of sustainability aspects - New solution approaches to solve large-scale problems	Current available computational tools	Enhanced decision-making capabilities
		Data-driven optimization and simulation-optimization approaches	- Integration of state-of-the-art optimization techniques with data analytics - On-line decision-making - Effective incorporation of uncertainty and risk assessment - Reduced model complexity for large-scale problems - Integration of high-level detail (simulation) with optimization techniques to find optimal or quasi-optimal solutions		
		Virtualization and simulation	- Improve operational performance - Simulation of scale-up processes before its implementation - Foster process safety opportunities		

Appendix D – Process design data

Table D.1 Process design data, including the minimum and maximum number of cycles, and the associated costs

p	t	Process design (j)	Min. nr. cycles (η_{pjlt}^{min})	Max. nr. cycles (η_{pjlt}^{max})	Variable cost (rmu) (α_{pjl}^{var})	Fixed cost (rmu) (α_{pjl}^{fix})	Process changes cost (rmu) (α_{pt}^{pc})
PA	0	D1L1_F1L1_R1L1	1	5	49.5	150	225
		D1L2_F1L2_R1L2	1	5	54.5	150	225
		D1L3_F1L3_R1L3	1	3	64.5	150	225
	1	D1L1_F1L1_R1L1	1	5	49.5	150	225
		D1L2_F1L2_R1L2	1	5	54.5	150	225
		D1L3_F1L3_R1L3	1	3	64.5	150	225
	2	D1L2_F1L2_R1L2	1	5	54.5	150	225
		D1L3_F1L3_R1L3	1	4	64.5	150	225
		D1L4_F1L4_R1L4	1	2	84.5	150	225
	3	D1L3_F1L3_R1L3	1	2	64.5	150	300
		D1L4_F1L4_R1L4	1	5	84.5	150	300
		D1L3_F1L3_R2L3	1	2	67.5	230	300
	4	D1L3_F1L3_R1L3	1	5	64.5	150	300
		D1L4_F1L4_R1L4	1	5	84.5	150	300
		D1L3_F1L3_R1L3_R2L3	1	5	84.5	300	300
	5	D1L3_F1L3_R1L3_R2L3	1	2	84.5	300	300
		D1L4_F1L4_R1L4	1	5	84.5	150	300
		D1L4_F1L4_R1L4_R2L4	1	3	104.5	300	300
	6	D1L4_F1L4_R1L4_R2L4	1	2	132	300	525
		D1L4_F1L4_R1L4	1	1	163	150	525
		D1L4_F1L4_R1L4_R3L4	1	1	162.5	600	525
	7	D1L4_F1L4_R1L4_R2L4	1	6	104.5	300	525
		D1L4_F1L4_R1L4	1	1	146	150	525
		D1L4_F1L4_R1L4_R3L4	1	5	107.5	600	525
	8	D1L4_F1L4_R1L4_R2L4	1	4	117.5	300	525
		D1L4_F1L4_R1L4	1	5	84.5	150	525
		D1L4_F1L4_R1L4_R2L4_R3L4	1	2	182.5	750	525
	9	D1L4_F1L4_R1L4	1	5	84.5	150	525
		D1L4_F1L4_R1L4_R2L4	1	6	104.5	300	525
		D2L4_F1L4_R1L4_R2L4	1	3	120	350	525
PB	0	D1L1_F1L1_R1L1	1	5	54.5	150	345
		D1L1_F1L1_R2L1	1	3	57	230	345
		D1L2_F1L2_R1L2	1	2	74.5	150	345
	1	D1L1_F1L1_R1L1	1	3	54.5	150	345
		D1L1_F2L1_R1L1	1	2	54.5	200	345
		D2L1_F1L1_R1L1	1	3	54.5	200	345
	2	D1L1_F1L1_R1L1	1	3	54.5	150	345

p	t	Process design (j)	Min. nr. cycles (η_{pjlt}^{min})	Max. nr. cycles (η_{pjlt}^{max})	Variable cost (rmu) (α_{pjl}^{var})	Fixed cost (rmu) (α_{pjl}^{fix})	Process changes cost (rmu) (α_{pt}^{pc})
		D1L2_F1L2_R1L2	1	2	74.5	150	345
		D1L1_F2L1_R1L1	1	3	54.5	200	345
		D1L1_F1L1_R1L1	1	5	54.5	150	450
	3	D1L2_F1L2_R1L2	1	5	74.5	150	450
		D1L2_F1L2_R2L2	1	3	77	230	450
		D1L1_F1L1_R1L1	1	5	54.5	150	450
	4	D1L2_F1L2_R1L2	1	5	74.5	150	450
		D1L2_F1L2_R2L2	1	4	77	230	450
		D1L2_F1L2_R1L2	1	5	74.5	150	450
	5	D1L2_F1L2_R2L2	1	5	77	230	450
		D1L3_F1L3_R1L3	1	3	129	150	450
		D1L3_F1L3_R2L3	1	2	154	230	675
	6	D1L3_F1L3_R1L3	1	5	129	150	675
		D1L2_F1L2_R1L2	1	1	123.5	150	675
		D1L3_F1L3_R2L3	1	5	117	230	675
	7	D1L3_F1L3_R1L3	1	2	178	150	675
		D1L4_F1L4_R1L4	1	2	258	150	675
		D1L4_F1L4_R2L4	1	3	234	230	675
	8	D1L3_F1L3_R1L3	1	5	129	150	675
		D1L4_F1L4_R1L4	1	2	258	150	675
		D1L4_F1L4_R2L4	1	3	234	230	675
	9	D1L4_F1L4_R1L4	1	2	258	150	675
		D1L3_F1L3_R1L3	1	5	129	150	675
		D1L1_F1L1_R1L1	1	4	101	150	300
	0	D1L1_F1L1_R2L1	1	4	104	230	300
		D1L2_F2L2_R2L2	1	1	147	280	300
		D1L1_F1L1_R1L1	1	3	101	150	300
	1	D1L1_F1L1_R2L1	1	2	104	230	300
		D2L1_F1L1_R1L1	1	2	103.5	200	300
		D1L1_F1L1_R1L1	1	2	101	150	300
	2	D1L1_F1L1_R2L1	1	2	104	230	300
PC		D2L1_F1L1_R1L1	1	3	103.5	200	300
		D1L1_F1L1_R1L1	1	4	101	150	420
	3	D1L2_F1L2_R1L2	1	3	163	150	420
		D1L2_F1L2_R2L2	1	5	144	230	420
		D1L1_F1L1_R1L1	1	5	101	150	420
	4	D1L2_F1L2_R2L2	1	5	144	230	420
		D1L2_F1L2_R1L2	1	3	163	150	420
		D1L2_F2L2_R2L2	1	5	147	280	420
	5	D1L2_F1L2_R2L2	1	5	144	230	420
		D2L2_F1L2_R2L2	1	2	193.5	280	420

p	t	Process design (j)	Min. nr. cycles (η_{pjlt}^{min})	Max. nr. cycles (η_{pjlt}^{max})	Variable cost (rmu) (α_{pjl}^{var})	Fixed cost (rmu) (α_{pjl}^{fix})	Process changes cost (rmu) (α_{pt}^{pc})
		D3L4_F3L4_R3L4	1	4	400	950	945
	6	D1L2_F1L2_R2L2	1	1	247	230	945
		D2L3_F2L3_R3L3	1	1	332	630	945
		D1L3_F1L3_R2L3	1	1	391	230	945
	7	D1L2_F2L2_R1L2_R2L2	1	1	270	350	945
		D2L3_F2L3_R3L3	1	2	278	630	945
		D2L3_F2L3_R2L3	1	1	324	330	945
	8	D1L3_F2L3_R3L3	1	4	248	580	945
		D2L3_F2L3_R3L3	1	1	332	630	945
		D2L4_F2L4_R3L4	1	2	438	630	945
	9	D2L3_F2L3_R2L3	1	1	324	330	945
		D1L3_F2L3_R3L3	1	4	248	580	945
		D1L1_F1L1_R1L1	1	5	111	150	4000
	0	D3L1_F1L1_R1L1	1	5	116	320	4000
		D1L1_F1L1_R2L1	1	5	115	230	4000
		D1L1_F1L1_R1L1	1	5	111	150	4000
	1	D1L1_F1L1_R2L1	1	5	115	230	4000
		D1L1_F2L1_R1L1	1	4	113.5	200	4000
		D1L1_F1L1_R1L1	1	5	111	150	4000
	2	D1L1_F1L1_R2L1	1	5	115	230	4000
		D1L1_D3L1_F1L1_R2L1	1	5	137	430	4000
		D1L1_F1L1_R2L1	1	5	115	230	4000
	3	D1L1_F1L1_R1L1	1	5	111	150	4000
		D1L1_F1L1_R1L1_R2L1	1	4	176	300	4000
		D1L1_F1L1_R2L1	1	5	115	230	4000
	4	D1L1_F1L1_R1L1	1	5	111	150	4000
PD		D1L1_F1L1_R1L1_R2L1	1	6	176	300	4000
		D1L2_F1L2_R2L2	1	4	199	230	4000
	5	D1L1_F1L1_R1L1	1	5	111	150	4000
		D1L1_F1L1_R2L1	1	5	149	230	4000
		D1L2_F1L2_R2L2	1	4	199	230	4000
	6	D2L2_F1L2_R2L2	1	5	184.5	280	4000
		D2L2_F2L2_R2L2	1	5	170	330	4000
		D1L2_F1L2_R2L2	1	4	199	230	4000
	7	D2L2_F1L2_R2L2	1	4	184.5	280	4000
		D1L4_F1L4_R2L4	1	2	549	230	4000
		D1L2_F1L2_R2L2	1	1	281	230	4000
	8	D1L3_F1L3_R1L3	1	2	427	150	4000
		D1L4_F1L4_R2L4	1	2	549	230	4000
		D1L2_F1L2_R1L2	1	2	222	150	4000
	9	D1L2_F1L2_R2L2	1	3	199	230	4000
		D1L3_F1L3_R1L3	1	1	427	150	4000

p	t	Process design (j)	Min. nr. cycles (η_{pjlt}^{min})	Max. nr. cycles (η_{pjlt}^{max})	Variable cost (rmu) (α_{pjl}^{var})	Fixed cost (rmu) (α_{pjl}^{fix})	Process changes cost (rmu) (α_{pt}^{pc})
PE	0	D1L1_F1L1_R1L1	1	2	159.5	150	2000
		D1L1_F1L1_R1L1_R2L1	1	4	213.5	300	2000
		D1L1_F1L1_R2L1	1	5	113	230	2000
	1	D1L1_F1L1_R1L1	1	5	109	150	2000
		D1L1_F1L1_R2L1	1	5	113	230	2000
		D1L1_F2L1_R1L1	1	5	111.5	200	2000
	2	D1L2_F1L2_R2L2	1	5	188.5	230	2000
		D1L1_F2L1_R1L1_R2L1	1	4	149	350	2000
		D1L1_F1L1_R1L1_R2L1	1	4	163.5	300	2000
	3	D1L2_F1L2_R2L2	1	5	188.5	230	2000
		D1L1_F2L1_R1L1_R2L1	1	3	149	350	2000
		D1L2_F2L2_R2L2	1	5	174	280	2000
	4	D1L2_F1L2_R2L2	1	5	188.5	230	2000
		D1L3_F1L3_R2L3	1	2	368.5	230	2000
		D1L2_F2L2_R2L2	1	5	174	280	2000
	5	D1L2_F1L2_R2L2	1	5	188.5	230	2000
		D1L2_F2L2_R2L2	1	5	203	280	2000
		D1L4_F1L4_R2L4	1	2	607	230	2000
	6	D1L2_F1L2_R2L2	1	2	268.5	230	2000
		D1L4_F1L4_R2L4	1	2	607	230	2000
		D1L3_F1L3_R2L3	1	3	368.5	230	2000
	7	D1L4_F1L4_R2L4	1	2	607	230	2000
		D1L2_F1L2_R2L2	1	1	302.5	230	2000
		D1L3_F1L3_R2L3	1	4	368.5	230	2000
	8	D1L4_F1L4_R2L4	1	2	607	230	2000
		D1L2_F1L2_R2L2	1	5	188.5	230	2000
		D1L3_F1L3_R2L3	1	3	368.5	230	2000
	9	D1L4_F1L4_R2L4	1	1	607	230	2000
		D1L4_F1L4_R1L4	1	1	695	150	2000
		D1L3_F1L3_R2L3	1	2	368.5	230	2000

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